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CONTENTS

Chemotherapy with the Sulfonamide Derivatives: General Principles 197
Francis G. Blake

Chemotherapy of Pneumonia 208
Norman Plummer

A Consideration of Some of the Toxic Effects of Sulfonamide Compounds, Particularly Sulfapyridine . 217
William S. Tillett

Hyperpituitarism and Hypopituitarism 227
Leo M. Davidoff

Hypertension—The Problem, The Study, The Future . 244
Stanford W. Mulholland

Library Notes:
Recent Accessions 256

Proceedings of Academy Meetings 257

In Memoriam, Hans Horst Meyer 260

Deaths of Fellows 261

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

APRIL 1940

CHEMOTHERAPY WITH THE SULFONAMIDE DERIVATIVES: GENERAL PRINCIPLES*

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FOLLOWING the introduction of the sulfonamide group of drugs as bacterial chemotherapeutic agents and their first reported clinical application by Foerster[1] in 1933, the use of these compounds in the treatment of infections in man very soon became so apparently successful that they were already widely used clinically before much was known concerning the scope and nature of their chemotherapeutic properties in experimental infections in animals, their mechanism of action, their toxicity, and the principles governing their absorption, distribution, conjugation and excretion. Numerous compounds appeared in rapid succession under a variety of confusing names with conflicting claims concerning their relative merits in this or that type of infection. Gradually, however, careful laboratory investigations began to parallel and influence clinical application, until latterly they have begun quite properly to precede the introduction of new compounds, prepared with the purpose of extending the usefulness of the sulfonamide derivatives in human disease.

* Presented January 4, 1940 at the Annual Meeting of The New York Academy of Medicine.
From the Department of Internal Medicine, Yale University School of Medicine.

Since the intelligent use of these drugs must be based upon an adequate understanding of their scope and mode of action and their pharmacological properties, it is my purpose in this general discussion to review the development of knowledge concerning these problems. I shall endeavor to point out their bearing on clinical therapeutics. Of necessity I must limit myself to the high-lights since the time available will not permit me to fill in much in the way of detail.

The sulfonamide group of drugs center around para-amino-benzene sulfonamide, first synthesized by Gelmo[2] in 1908. Though not the first compound introduced into chemotherapy, it has become the hub of the wheel and now bears the medical designation, sulfanilamide. For the purposes of the present discussion its derivatives may be conveniently placed in two groups.

The first group, which includes the original prontosil used by Domagk,[3] consists of those derivatives in which substitutions have been made in the para-amino group. Of these the more important are the azo dyes prontosil (Mietzsch and Klarer,[4] 1932; Domagk,[3] 1935) and the more soluble neoprontosil (Domagk,[5] 1935), and benzyl sulfanilamide (septazine, Goissedet et al,[6] 1936).

The second group consists of those derivatives in which substitutions have been made in the sulfonamide group at the other end of the benzene ring leaving the para-amino group free. Among these may be mentioned sulfanilyl sulfanilamide (Rosenthal et al,[7] 1937) and its dimethyl derivative (Domagk,[8] 1937), diamino-diphenyl sulphone (Buttle et al,[9] 1937), sulfapyridine (Whitby,[10] 1938), and sulfathiazole (Fosbinder and Walter,[11] 1939) and its methyl derivative sulfamethylthiazole (Herrell and Brown,[12] 1939) recently introduced and now being submitted to experimental investigation in the laboratory and the clinic.

The reason for grouping the sulfonamide derivatives in this fashion, which will, perhaps, become more evident as I proceed, is because it would appear to bear at least some relation to breadth and effectiveness as well as mode of therapeutic action.

Comparative studies in experimental animals on the protective action of the sulfonamide group of drugs, and *in vitro* observations on their bacteriostatic and bactericidal properties, beginning with the original observations of Domagk[3] on the curative action of prontosil on β-hemolytic streptococcal infection in mice down to the most recent observations on sulfamethylthiazole[12] on staphylococcal infections have covered

a wide range of bacteria and viruses. At first glance the results reported by various investigators often appear conflicting, no doubt in large part due to numerous variables which inevitably occur in experiments of this kind before an acceptable, standard technique has been evolved.

In spite of these difficulties certain high-lights stand out, which may serve to bring some degree of order out of the apparent confusion, even though many points still remain at issue.

The first significant experimental observations were, of course, those of Domagk,[3,5] that the azo dyes, prontosil and neoprontosil, though exerting no demonstrable bactericidal or bacteriostatic action *in vitro,* were nevertheless highly effective *in vivo* against virulent hemolytic streptococci, 100 per cent of treated mice surviving 10 m.l.d. for seven days in his first recorded experiment. These observations have been amply confirmed[13] by numerous subsequent observers, though in general without quite such perfect results.

The second highly important contributions were those of the Tréfouëls[14] and their collaborators, who showed that sulfanilamide by itself without the azo linkage was not only effective against hemolytic streptococcal infections in mice but also possessed active bacteriostatic properties *in vitro.* These observations provided the basis for the now widely accepted view that the azo dyes, prontosil and neoprontosil, are changed in the animal body and owe at least the major portion of their activity to the liberation of sulfanilamide, which is the active component, a view well supported by the studies of Colebrook, Buttle and O'Meara,[15] Fuller,[16] and Long and his collaborators.[17]

If this be correct, sulfanilamide weight for weight should be more effective as a chemotherapeutic agent than prontosil, neoprontosil and benzyl-sulfanilamide, provided variations in absorption are not so great as to render comparisons invalid. Though the pitfalls in such comparisons are numerous and there is not complete agreement, I believe it safe to state that the majority of workers have recorded experiments indicating that sulfanilamide, weight for weight, is at least equivalent to or superior to the prontosils and benzyl compounds, so far as chemotherapeutic effectiveness against hemolytic streptococci is concerned. Not only does this appear to be so with hemolytic streptococci but also in the case of many other bacteria. Among them may be included meningococci, pneumococci, staphylococci, Friedländer's bacillus and brucella.

If we turn now to the other group of compounds in which substitu-

tions in the sulfonamide group have been made, the picture appears quite different. Here we find compounds which are at least equivalent to, if not superior to, sulfanilamide in experimental streptococcal and meningococcal infections. At the same time the scope of their effectiveness appears to be wider. Conspicuous among these is sulfapyridine, the superiority of which in pneumococcal infections is already well established. Animal experiments, furthermore, suggest that it is more effective than sulfanilamide in staphylococcal[18] and Friedländer's bacillus[13] infections. Two newcomers, still in the stage of experimental investigation, are sulfathiazole and sulfamethylthiazole. In preliminary studies by McKee, Rake, Greep and van Dyke,[19] sulfathiazole would appear at least equivalent to sulfapyridine, so far as hemolytic streptococci, pneumococci, and meningococci are concerned, while sulfamethylthiazole may perhaps be even more effective in staphylococcal infections,[12] though further data are necessary to confirm this.

Although comparative experiments would appear to suggest that the differences in scope and effectiveness exhibited by these two groups of sulfonamide derivatives are largely quantitative, this cannot be accepted as proved at present because standard methods for comparative assay have not been used. As emphasized by Marshall,[20] strains of organisms, size of inoculum, amount, spacing and method of dosage, duration of therapy and period of observation have varied so much from worker to worker that accurate quantitative comparison is impossible with active compounds having different ratios of absorption and excretion.

Whether the differences exhibited indicate actual qualitative differences in specificity for different organisms is likewise impossible to answer with certainty at present. The much greater effectiveness of sulfapyridine against the pneumococcus, for example, would suggest specificity, but since there is some evidence that it is also more effective against hemolytic streptococci,[10,13,18] staphylococci[13,18] and Friedländer's bacilli,[13] this may be merely a quantitative difference.

The relative importance of the amino group and the sulfonamide group in determining chemotherapeutic activity likewise cannot be stated dogmatically at present. Active compounds, with rare and somewhat dubious exceptions, either have a free amino group in the para-position to the sulfonamide group or a substituted group (nitro group or azo linkage) which is readily changed to an amino group in the animal body. Substitutions which do not permit change to an amino group,

e.g., acetyl sulfanilamide, in general, appear to be inactive.

Since, by definition the group of compounds under discussion contain sulfur in the sulfonamide group it is irrelevant to enter into a discussion here as to whether sulfur is an essential component for chemotherapeutic activity, though it may be remarked in passing that this is unlikely (Rosenthal, Bauer and Elvove[21]).

Whatever the ultimate solution of the foregoing problems may be, the clinical significance of these comparative *in vivo* and *in vitro* studies of the sulfonamide derivatives against various bacteria is obvious, since they point the way to the selection of the most effective drugs among the various compounds available. Furthermore, they suggest at least that the road to further improvement in scope and effectiveness of action lies along the way of substitutions in the sulfonamide group.

It hardly need be pointed out, however, that other factors besides relative chemotherapeutic efficiency in mice and bacteriostatic activity in the test tube may of necessity modify the selection of the most suitable drug for practical therapeutics in man, such factors as primary toxicity, absorbability, and human idiosyncrasy to untoward reactions, to mention a few.

For example, the experimental studies indicate clearly the superiority of sulfapyridine over sulfanilamide in pneumococcal infections, an observation which has found ample confirmation in the clinic. In hemolytic streptococcal infections on the other hand, the fact that sulfapyridine seems to possess some superiority in laboratory studies, would hardly justify at present the complete abandonment of sulfanilamide in favor of sulfapyridine, in view of the poorer absorbability, greater variability in acetylation and greater tendency to induce untoward reactions, such as nausea, vomiting and hematuria, exhibited by sulfapyridine. In the end, of course, carefully controlled studies in patients, so well illustrated by the studies of the last year on sulfapyridine in lobar pneumonia, must determine the issue in favor of this or that compound in any given infection.

It is now so well established by the work of numerous investigators that the therapeutic activity of the sulfonamide compounds is dependent upon their bacteriostatic action, rather than upon a capacity to stimulate the defensive mechanisms of the host, that it seems hardly necessary in this discussion to marshal the evidence in support of this view. Nor does it seem profitable to enter into a discussion of the several theories

concerning the mechanism by which bacteriostasis is brought about, since none of them has as yet attained the position of final proof.

A few points with clinical implications, however, emerge from the welter of *in vitro* and *in vivo* studies on mechanism of action which may be briefly touched upon.

The failure of the azo dyes to exhibit bacteriostatic action *in vitro* as contrasted with sulfanilamide and those derivatives in which substitution has been made in the sulfonamide group has already been mentioned and its implications pointed out.

In vitro experiments, principally on hemolytic streptococci but also on other bacteria, with concentrations of sulfanilamide equivalent to those attained in the blood of patients and with a suitably small initial inoculum, have commonly resulted after an initial lag period in variable degrees of bacteriostasis without true bactericidal effect. In the presence of whole blood, as contrasted with blood deprived of leukocytes, prompt killing of streptococci occurs. Similarly a much greater bacteriostatic action and frequently a bactericidal action in the presence of whole blood has been found in our laboratory by Dr. Haury with sulfapyridine and staphylococci. These observations have strongly suggested that coöperative activity on the part of phagocytic and perhaps other immunity mechanisms of the host is important or essential in the final recovery of patients being treated with the sulfonamide drugs. Numerous animal experiments, among others those of Gay and Clark[22] in streptococcal infection in rabbits and Menefee and Poston[23] on brucella infections in guinea pigs, strongly support this view. When taken in conjunction with the oft repeated observation, particularly in streptococcal and staphylococcal infections, that relapse of infection with ultimate death often occurs in a considerable proportion of experimental animals following cessation of treatment, this fact assumes a position of significant importance in human therapeutics, particularly in those infections which do not naturally run a relatively brief, self-limited course to recovery.

To cite specific examples, facial erysipelas in adults in general runs a relatively short, self-limited course. It responds dramatically to sulfanilamide therapy and relapses are exceedingly rare even though therapy be discontinued relatively soon after the temperature has fallen to normal. By and large the same may be said to be true in lobar pneumonia treated with sulfapyridine, provided treatment is carried till the 7th to 9th day from onset, at which time the immunity mechanism commonly

comes into operation. Erysipelas of the new-born, on the other hand, usually runs a progressive course with generalization of the infection and ultimate death. Likewise responding brilliantly to early treatment, relapse is apt to occur with early cessation of treatment.

Streptococcal sinusitis, mastoiditis and sepsis, gonococcal prostatitis and staphylococcal pyemia provide other examples in which initial response to chemotherapy may give a false sense of security, masking the fact that infection is still smoldering in local suppurative foci, ready to flare up when chemotherapy is discontinued, a problem ably discussed recently by Converse[24] in the case of otitic infections.

Obviously, the problem of combined chemo and serum therapy versus chemotherapy alone in pneumococcal, meningococcal, and gas bacillus infections as well as others, is brought sharply into focus by the laboratory studies which indicate the coöperative role of immunity mechanisms in fortifying the chemotherapeutic action of the sulfonamide derivatives, but lack of time and the sparsity of adequately controlled comparative studies in man induce me to pass it by without further discussion. Nor shall I comment on the important observations of White and Parker[25] on the influence of temperature and those of Lockwood[26] on the influence of nutritional environment on the bacteriostatic action of sulfanilamide, since their possible clinical significance is not yet clearly apparent, though the latter, as suggested by Lockwood, may have an important bearing on the tendency for bacteria to survive in walled off suppurative lesions unless these be surgically drained.

Pharmacological studies, conspicuously those of Marshall[20] and his collaborators, have likewise contributed much of value to the practical application of chemotherapy in man. These studies have been concerned particularly with problems of toxicity, absorption, distribution in the body, conjugation to the inactive acetyl derivatives, and excretion. They have had an especially useful bearing on problems of amount and spacing of dosage in relation to establishment and maintenance of adequate blood levels. The development of Marshall's method[27] for the quantitation of blood concentrations of total and free sulfonamide compounds has provided not only a useful guide to dosage but has made it possible to acquire information concerning the relation of blood levels to therapeutic effect and untoward reactions in patients under treatment.

Comparative observations on blood concentrations following a single dose *per os* of 0.1 gm./K in dogs indicate a considerably more rapid

absorption of sulfanilamide than of sulfapyridine or sulfathiazole. At the same time the percentage of administered drug recovered in the urine during the ensuing twenty-four hours indicates a much more complete absorption and a somewhat more rapid rate of diffusion and excretion for the former. These observations find their counterpart in clinical observations showing the range of blood concentrations of sulfanilamide[27] and sulfapyridine[28] and a few recent observations on sulfathiazole[29] four hours after an initial dose *per os*. They indicate the greater urgency for an initial intravenous treatment with sulfapyridine than is the case with sulfanilamide in critically ill patients in whom it is desirable to establish an adequate concentration in the blood and body fluids as rapidly as possible.

Furthermore, the more rapid rate of excretion in the case of sulfanilamide suggests that treatment every four hours, day and night, is perhaps more essential for the maintenance of continuously adequate blood levels with this drug than may be the case with sulfapyridine. At least it has been our experience that treatment at six hour intervals with sulfapyridine will, in many instances, maintain an adequate blood level, once established, and even at eight to twelve hour intervals under parenteral treatment[30] by hypodermoclysis or intravenously. The problem is complicated in man, by so much individual variation from patient to patient that wider spacing of dosage with sulfapyridine than the customary four hour interval cannot at present be advocated as a routine but should be resorted to only when the presence of the higher range of blood levels indicates that it is permissible in a particular individual.

Pharmacological observations on the conjugation of sulfanilamide in animals have shown so much species difference in the capacity to convert sulfanilamide to the inactive acetyl compound that it has been found necessary to study this problem in man. Marshall[27] found that 10 to 20 per cent of the total sulfanilamide in the circulating blood was in the conjugated form and Stewart, Rourke and Allen[31] have shown that the ratio between free and acetyl sulfanilamide varies considerably from individual to individual. In the case of sulfanilamide, however, the degree of acetylation in man and individual variation would not appear to be of sufficient magnitude to be of clinical import and in practical therapeutics may be disregarded. A few preliminary observations[29] in patients treated with sulfathiazole and sulfamethylthiazole suggest that the same may hold for these compounds, but more extensive studies are

necessary before the possible range of individual variation will be known.

With sulfapyridine, on the other hand, the picture is quite different. The degree of acetylation may vary unpredictably over a wide range from patient to patient.[30,32] Recognition of this fact is of great importance in therapeutics if blood levels are to be used as a guide to amount and spacing of dosage, for a low or falling concentration of free sulfapyridine may be mistakenly regarded as an indication for increasing dosage when, in fact, the total concentration is rising with an increasing proportion of acetyl sulfapyridine present. On more than one occasion I have seen this mistake made, to be followed by gross hematuria, colic, temporary anuria and azotemia.

I have used the phrase adequate blood concentration without specifying what that may be, and I must confess to some degree of uncertainty concerning this, an uncertainty which has arisen from the now well established and perhaps unexpected finding that many cases of pneumococcal lobar pneumonia respond as promptly and dramatically to sulfapyridine with blood levels of free sulfapyridine under 5 mg. per cent as do those with higher levels.[30] Quite early in the use of sulfanilamide in hemolytic streptococcal infections, 10 mg. per cent or thereabouts was somewhat arbitrarily advanced as a desirable and necessary blood concentration for satisfactory therapeutic results and there can be no doubt that experience has shown that blood concentrations at this level are effective. Since adequate comparative data on the possible effectiveness of lower blood concentrations are not available, it is of no value to discuss the point, further than to suggest that it might be desirable to reëxamine this question in the light of the results with sulfapyridine in pneumococcal pneumonia.

I have purposely not touched upon the general problems of toxicity and untoward reactions since they are to be discussed by a subsequent speaker on this program. If I have disappointed you by using the subjunctive more than you would like, I can only say that it has seemed to me the part of wisdom to be neither too positive nor too dogmatic in our present state of fragmentary, though rapidly increasing knowledge concerning the general principles involved in chemotherapy with the sulfonamide derivatives. That the future of chemotherapy will witness advances equal to or more brilliant than those of the last few years, there seems little doubt.

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CHEMOTHERAPY OF PNEUMONIA*

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MANY reports have appeared in the literature describing the use of sulfapyridine in the treatment of pneumonia. It is significant that all of these reports from the first one by Evans and Gaisford have presented favorable evidence. Already it is possible to assemble a series of cases, fully enough studied and of sufficient size so that from it some rather definite conclusions on the efficacy of the drug may be obtained. The gross mortality rate of lobar pneumonia varies greatly from year to year, even in the same locality or in the same institution. However, when similar age groups are included, it is safe to compare the results of treatment in different series of the same type, and it is even more reliable when the comparison is between bacteriemic or non-bacteriemic cases of a particular type.

The striking reduction in mortality rates in the more common types of pneumonia offers the most convincing evidence of the value of sulfapyridine. In order to make an analysis by types, it is possible to collect from the literature 966 cases of pneumococcus pneumonia in adults, in this geographical area, treated with sulfapyridine. A small percentage of these patients received anti-pneumococcus serum also, but it is impossible to separate these from the rest of the group. For comparison we are fortunate in having available the very large series of cases collected by Heffron in which he has attempted to establish the fatality rates for lobar pneumonia and for the different types in the United States and Canada.

Type I pneumonia, in Heffron's series of 2,314 cases without specific therapy, had a mortality rate of 29.0 per cent. During the past year, in the United States and Canada 193 cases of type I infection treated with sulfapyridine have been reported. Twelve deaths occurred, giving a fatality rate of 6.2 per cent. Heffron's series includes 351 cases of

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type I pneumonia with bacteriemia, and in this group the mortality rate was 58.1 per cent. Contrast this figure with one of 13.9 per cent in forty-three bacteriemic type I cases treated with sulfapyridine.

The results obtained in type II and type III pneumonias are even more impressive because these diseases never showed the marked response to specific serum that has been demonstrated in type I and in some of the higher types. There have been sixty-three patients with type II infection treated with sulfapyridine with four deaths, a mortality of 6.3 per cent. Only seven of these patients showed positive blood cultures, and of these two died. Heffron shows mortality rates of 36.6 per cent in untreated type II pneumonia, and 74 per cent for bacteriemic type II. A recent communication from Anderson and his associates in Glasgow on seventy cases of type II pneumonia treated with sulfapyridine shows a death rate of 8.0 per cent. Twenty-five of the seventy cases, or 36 per cent, also had bacteriemia, and of these 16 per cent died. Type III, the most dreaded of the types, in Heffron's cases shows a fatality rate of 46.0 per cent in the gross series, and 86.1 per cent in the bacteriemic group. In the sulfapyridine series, there are 156 type III pneumonias with a mortality of 15.4 per cent, and in this group eighteen had bacteriemia, and 38.9 per cent died.

The total series of 966 pneumococcus pneumonias in adults treated with sulfapyridine shows a mortality rate of 8.5 per cent as compared with 32.8 per cent in some nineteen thousand similar cases without specific treatment analyzed by Heffron. One hundred and twenty bacteriemic cases including all types gave a mortality percentage of 26.7 to be contrasted with 61.8, Heffron's calculated figure.

The clinical response to sulfapyridine is almost as remarkable as the reduction in mortality rate. With almost constant regularity the temperature drops to normal within 24 to 36 hours after therapy is instituted. The pulse becomes slower and less bounding, the respiration slower and more normal. At this stage, the patient no longer seems critically ill, but does remain toxic and uncomfortable. The color is poor; he is restless and quite often delirious. He may continue to complain of headache; usually has marked anorexia and frequently nausea. To be sure, some of these symptoms are toxic manifestations of the drug. The physical signs of pneumonia may continue to develop or may be abruptly aborted.

The most striking feature of the response is the consistency with

which the blood cultures in bacteriemic cases become negative following sulfapyridine. This usually occurs even in cases of overwhelming blood stream infection. In our New York and Bellevue Hospital series, only four out of sixty bacteriemic cases had positive blood cultures following the institution of sulfapyridine therapy. One of these had a definite endocarditis and another a meningitis and suspected endocarditis. The most miraculous recoveries following sulfapyridine are those that have occurred in the bacteriemic cases with high colony counts. Two of our type V pneumonias recovered, both late cases, with blood-culture plates showing innumerable colonies (over 1,000 per cc.). One of these patients had sulfapyridine and serum and the other had sulfapyridine alone. A type III patient with 250 organisms per cc. in the blood recovered from his pneumonia, although he died many months later following surgical treatment of a lung abscess. Graham and his associates in Toronto described a type III pneumonia with 450 organisms per cc. that promptly recovered after sulfapyridine alone. In pneumococcus bacteriemia, it must be admitted that specific serum, even type I, has not shown the dramatic result produced by sulfapyridine.

The effect of sulfapyridine on the incidence and the course of other complications of pneumonia cannot yet be ascertained. However, a few significant observations have already been recorded. Pneumococcus meningitis complicating pneumonia, hitherto almost universally fatal, has been found to respond to sulfapyridine or similar drugs in a few cases. Hodes and his associates have reported one such recovery. Endocarditis, fortunately a rare complication, occurred only once in our sulfapyridine series. The blood could not be kept sterile in this case, even when high blood levels were obtained, and the patient died having developed meningitis also. Empyema has been encountered a number of times, but whether its incidence or course is significantly affected by sulfapyridine remains a moot question. The fact that the prognosis in empyema is so much more serious when it occurs during the height of the pneumonia when the more generalized pneumococcus infection is still active, and that these active infections are so definitely aided by the drug, would indicate that empyema as a whole would be benefited by this treatment. Furthermore, the mortality rate in our own and the reported cases of empyema is unusually low, but the series is not large enough to give significance to conclusions that might be drawn from it.

Secondary infections have been recognized more frequently since

we have been using chemotherapy. For example, a patient with type III pneumonia and bacteriemia, later showed Streptococcus viridans and then staphylococcus in the blood, but he eventually recovered. In several cases of pleural effusion following pneumonia, Streptococcus viridans has been cultured from the fluid. Lung abscess, which is probably a secondary infection, has been encountered several times. It is quite likely that in the future we will see sequelae of pneumonia and pneumococcus bacteriemia that we have not seen in the past—the sequelae that will occur in that group of patients who formerly would have died. Furthermore, there is the supposition that in individuals of a high bacterial susceptibility, while we arrest the primary pneumococcus infection, we do not control the secondary invaders.

Certain of the atypical pneumonias, which in the past have been so difficult to treat, have responded dramatically to sulfapyridine therapy. A particular highlight in our experience of the past year has been that of observing the response in some of the most unfavorable cases of pneumonia complicating heart disease and occurring in elderly individuals. We have had striking recoveries in pneumonias complicating bronchiectasis and asthmatic bronchitis and emphysema. Recently, Hinshaw reported enthusiastically on the treatment of postoperative pneumonia at the Mayo Clinic with sulfapyridine. A number of articles have appeared on the chemotherapy of childhood pneumonia, indicating a lower mortality, fewer complications, and a more prompt recovery.

Undoubtedly, there are forms of acute pneumonia that do not respond to sulfapyridine. The group of atypical pneumonias, variously designated as virus pneumonias or atypical pneumonitis can probably best be diagnosed by a failure to respond to sulfapyridine or related drugs. In our very limited experience, the course of tuberculous pneumonia or tuberculous pleurisy with effusion is not altered by sulfapyridine. It does, however, have a wide scope of action in the common pyogenic infections, and among the different types of pneumococcus there seems to be no variation in effect. On the other hand, occasionally a strain of pneumococcus, regardless of type, may be found to be sulfapyridine resistant. Up to the present time, sulfapyridine-fastness has been demonstrated clinically infrequently, and most of the deaths have occurred in instances of serious systemic disorder, inadequate therapy, or overwhelming infection at the start of treatment.

The dosage of sulfapyridine remains empiric. No definite correla-

tion between the dosage or the blood level of sulfapyridine and the clinical response has been ascertained. Some of the most prompt recoveries have occurred with a small total dosage and with low blood level readings. At Bellevue Hospital we are continuing to use the dosage recommended by Evans and Gaisford in their original article, i.e., 2 gm. as an initial dose, followed by 1 gm. every four hours. Sixteen grams suffice for most of the uncomplicated cases. Some investigators have used a higher initial dose and some have given a much larger total amount. Our impression is that the response is no better with the larger dosage, and the patients seem to tolerate the drug more satisfactorily when the blood level is increased less abruptly. Furthermore, the impression is obtained from going over reports, that the incidence of the serious toxic reactions is higher in the series treated with the larger dosage.

LEGENDS FOR CHARTS

Chart I. This is the temperature curve of a 60 year old female patient admitted to New York Hospital on the sixth day of her illness. She had had fever, cough, and rusty sputum for 6 days and had been moderately jaundiced for 2 days. The physical signs and x-ray film showed consolidation of both upper lobes and resolving pneumonia of the right lower lobe. The jaundice was considered to be secondary to the acute pneumonia. The sputum yielded type VII pneumococci. Because of the acuteness and the extent of the pulmonary disease, in spite of the jaundice, sulfapyridine was instituted in the usual dosage shortly after admission. On the day following admission the blood culture was found to be positive. Sulfapyridine was continued until a total of 24 gm. had been administered. During this time, the temperature dropped, the blood culture became negative, and the jaundice subsided. The clinical improvement was steady, although the temperature remained low-grade and the white count elevated for several days. Recovery was finally complete. Cholecystograms made during convalescence, proved to be normal.

Chart II. This shows the chart of a 41 year old man, who had cirrhosis of the liver and acute Friedländer's bacillus pneumonia of the right upper lobe and part of the right lower lobe. He was given 2 gm. of sulfapyridine shortly after admission, and then 1 gm. every 4 hours for 9 days, then 0.5 gm. every 4 hours for 3 days. A total of 58.5 gm. was administered. The admission blood culture was negative, but the blood cultures on the second and fifth days grew type B, Friedländer's bacilli. Later blood cultures were negative. Sulfapyridine was given in the face of known liver disease and severe icterus. There was at first an increase and then a clearing of the icterus, but there was no other evidence of aggravation of the liver condition. During the first seven days of sulfapyridine therapy, the white blood cells increased from 4,200 to 24,000, but the hemoglobin dropped from 82 to 60 per cent. This patient has recovered from the acute pneumonia, but has developed a chronic Friedländer's bacillus abscess of the lung. On postural drainage, the abscess has reduced greatly in size, and at the present time we feel that the ultimate prognosis is quite good.

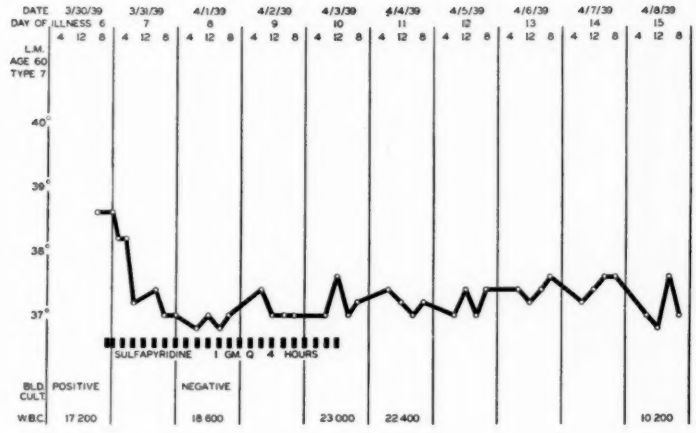

CHART I

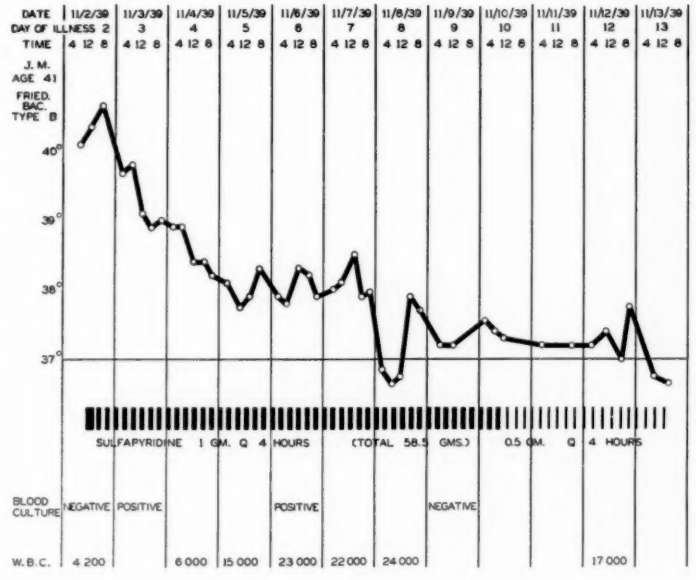

CHART II

Sulfapyridine has been administered by mouth in most of our cases. Attempts to give the drug by rectum have failed because the absorption is either very small or absent entirely. Blake and Haviland have dissolved 2 gm. of sulfapyridine in 1 liter of 5 per cent dextrose in saline solution by heating the preparation nearly to boiling, and have used this intravenously or by hypodermoclysis. Following Blake's method, the chemists at the Lederle Laboratories have been able to prepare for us a solution of 10 per cent sulfapyridine in 50 per cent glucose. This we have given intravenously, orally, and rectally without any reactions other than would be expected from a given concentration of sulfapyridine in the blood. However, when given rectally, similar to sulfapyridine, there is very slight absorption. When given intravenously, the free sulfapyridine blood content rises immediately to a level of about 2 mg. per cent (when 2 gm. is given), and falls within an hour to an almost negligible concentration. When given orally, blood levels

LEGENDS FOR CHARTS

Chart III. This shows the chart of a 46 year old man, admitted to New York Hospital a few hours after the onset of acute respiratory symptoms with bloody sputum. Physical examination and x-ray revealed pneumonia of the right lower lobe. The sputum showed type III pneumococci. The blood culture taken on admission was sterile. The urine analysis on admission was normal. Sulfapyridine was started shortly after admission with 2 gm. as the initial dose and then 1 gm. every four hours. The temperature dropped rapidly and the respiratory symptoms subsided promptly. On the second day after admission, after 11 gm. of sulfapyridine had been administered, there was sudden pain in the left side of the abdomen and in the left flank. The urine was found to be grossly bloody. Sulfapyridine was discontinued. On the next day an intravenous pyelogram showed a negative stone in the left kidney. Two days later, cystoscopy revealed numerous small concretions on the floor of the bladder and at the ureteral orifice. The hematuria and pain subsided in three days. Later pyelograms and kidney studies were negative.

Chart IV. This is the chart of a 62 year old man admitted to New York Hospital on the seventh day of acute symptoms of fever, pain in the right chest, and cough. The sputum showed type V pneumococcus. The physical and x-ray findings were those of lobar pneumonia of the right upper lobe and the upper part of the right lower lobe. Sulfapyridine was started on admission. The following day when the blood culture, taken on admission, showed over 2,000 organisms per cc., serum was administered in large amounts, to a total of 390,000 units. There was marked clinical improvement for several days, but then the temperature rose moderately, although sulfapyridine was continued until the eighth day after admission. On the ninth day empyema was diagnosed. The fluid revealed type V pneumococci. Three thoracenteses were done and on the twentieth day after admission a closed tube drainage was instituted, following which the convalescence was rapid and uneventful. This shows the recovery of a patient treated late in the disease when an overwhelming bacteriemia was present. Such a recovery heretofore in our experience had never been observed.

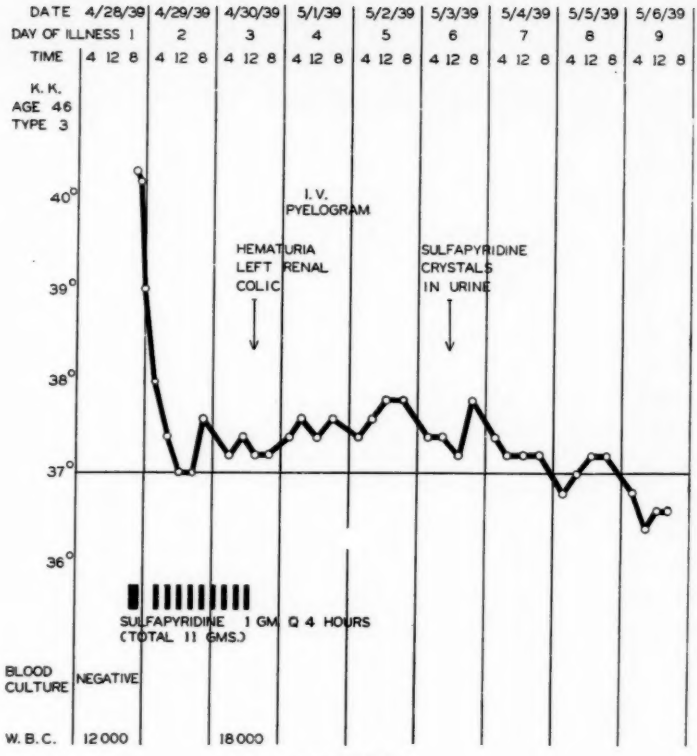
DATE 4/28/39 4/29/39 4/30/39 5/1/39 5/2/39 5/3/39 5/4/39 5/5/39 5/6/39
DAY OF ILLNESS 1 2 3 4 5 6 7 8 9
TIME 4 12 8 4 12 8 4 12 8 4 12 8 4 12 8 4 12 8 4 12 8 4 12 8 4 12 8
K. K.
AGE 46
TYPE 3
40°
39°
38°
37°
36°
I. V. PYELOGRAM
HEMATURIA LEFT RENAL COLIC
SULFAPYRIDINE CRYSTALS IN URINE
SULFAPYRIDINE 1 GM Q 4 HOURS (TOTAL 11 GMS.)
BLOOD CULTURE
NEGATIVE
W. B. C.
12 000
18 000

CHART III

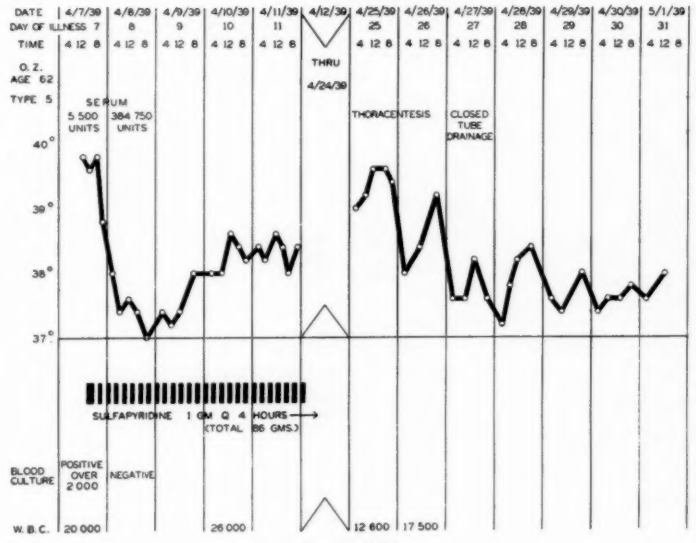

CHART IV

similar to those obtained by giving pure sulfapyridine by the same route, are procured, but the curve rises more slowly, reaching its peak in 24 hours instead of 12 hours. In fifty patients who have been treated with the glucose and sulfapyridine by mouth, using the usual dosage of 2 gm. initially and then 1 gm. every 4 hours, it is our impression that the same clinical response has occurred with considerably less nausea and vomiting. This finding confirms again our impression that the drug is tolerated better when the level of the blood rises more slowly.

Sodium sulfapyridine has been used intravenously in a few cases when absorption of sulfapyridine from the gastrointestinal tract has been unsatisfactory or when prompt action of the drug has been imperative. Our findings have been in agreement with those reported by Marshall and Long. Also, in a few cases we have confirmed the results reported by Gaisford, Evans, and Whitelaw following the administration of sodium sulfapyridine intramuscularly. Even though sodium sulfapyridine solution is highly alkaline, when given carefully into the deep intramuscular tissue there is only a slight local reaction and the absorption is satisfactory. This mode of treatment, however, is not to be recommended when sulfapyridine can be given by mouth. We have had very little experience in the use of the sodium salt by rectum, but there is mention in the literature that it is regularly absorbed and well tolerated when given this way.

In conclusion, I cannot refrain from making a few remarks regarding the present status of serum in the treatment of pneumonia. It has been shown over and over again that specific serum has value in pneumonia. On the other hand, there are recoveries after sulfapyridine that we would not expect after serum. It is fair to assume that there are some lives that serum will save which sulfapyridine will not. The exact sphere of each of these two agents has not yet been ascertained. Whether a combination of sulfapyridine and serum is a more efficient and more reliable treatment than sulfapyridine alone is an immediate problem for clinical investigation. It seems inevitable that some chemicals will be discovered which are even more effective against disease than sulfapyridine. Charts of four interesting cases are herewith presented.

A CONSIDERATION OF SOME OF THE TOXIC EFFECTS OF SULFONAMIDE COMPOUNDS, PARTICULARLY SULFAPYRIDINE*

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IT IS axiomatic of pharmacology that drugs are poisons and that the ultimate effect of the reagents is upon the cells of the body. Under controlled conditions, the stimulation or modification of cellular activity may be turned to great advantage in abnormal conditions of sickness. In infections this type of problem is particularly unique since the bacterial cells need to be destroyed but the cells making up bodily structure need to escape destruction. One of the reasons for the limited success of the chemotherapy of bacterial infections has formerly rested upon the fact that the so-called antiseptics were no respectors nor selectors of cells, with the result that the cells of the body were destroyed along with the bacterial cells. Even the relatively more successful kinds of reagents such as those with a mercurial base act through combination with the protoplasmic protein of the cellular structure. These chemicals are, therefore, in a sense, anatomical poisons in that they alter constituents of anatomical structure. Consequently, since proteins constitute such a large percentage of bodily structure, the quantitative extent of union between the types of bactericidal agents, just mentioned, and bacterial protoplasm could not be very effectual in competition with the enormous excess of body protoplasmic protein available for combination with the mercurial compounds.

Without entering into a consideration of the mechanism of the action of reagents of the sulfonamide series it seems highly likely that the effect is through destruction or impairment of some physiological activity of bacteria which is necessary for viability or virulence. Since, therefore, types of cells have individual physiological processes, irrespective of whether they be bacterial or part of the body mosaic, it

* Presented January 4, 1940 at the Annual Meeting of The New York Academy of Medicine.

appears that with the sulfonamide group of drugs an instrument is at hand which has selective possibilities. In combating infections the physiological poisons hold great promise as compared to the anatomical poisons. The sulfonamide drugs are, however, short of being absolutely ideal because patients receiving the drugs are subject to certain toxic manifestations, although remarkably—and in many instances dramatically—aided in overcoming the infection.

The rate of accumulation of literature in such an important subject is so considerable that data collected at one time are liable to be out of date within a very short period. For example, the earliest few articles on the treatment of pneumonia with sulfapyridine gave no special consideration to hematuria. We have now come to learn that this is a toxic manifestation of possibly greatest importance. Conversely, matters of particular early interest, such as effects on hydrogen ion equilibrium and even cyanosis, appear now to be looked upon less seriously. It is apparent, therefore, that an attempt at a statistical analysis of the frequency of the several toxic effects would at this time be premature. Indeed to attempt to list all the different kinds of reactions is unsatisfactory because, in addition to variations in published reports, innumerable individual personal experiences of physicians have not yet been consolidated into uniform findings.

I should like, therefore, to review the general order of magnitude, based on current information, of certain selected toxic effects, to comment on the mechanisms in so far as they are known, and to point out certain individual findings which have not yet received widespread attention but which warrant further inquiry and observation, because of the practical clinical questions which they provoke.

Among the drugs containing the sulfonamide configuration there appear to be certain toxic manifestations which are a denominator common to all of them that have been tried up to the present time, and, in addition, there are particular manifestations peculiar to the individual compounds. It has always been an interesting fact that the pharmacological action of drugs cannot be regularly predicted on the basis of chemical structure. With the increasing number of sulfonamide derivatives which are constantly being presented for clinical use, it becomes necessary to look for individual and unsuspected toxic manifestations as well as the ones already recognized.

The actions of sulfapyridine will be the chief subject for this dis-

cussion with appropriate reference to sulfanilamide. Without itemizing all the untoward reactions, the striking toxic effects which I should like to consider, center around the central nervous system, the hematopoietic system, and the urinary tract.

Central Nervous System

Mental disturbances have been noted frequently but have usually been mild in degree, taking the form of confusion, restlessness, dizziness, irritability or lassitude, and, in some instances, hallucinations. The degree and nature of the psychic disorders are not always easily measured because severe acute infections themselves may contribute an element of delirium. So far as I am aware no refractory psychiatric sequelae have persisted after cessation of the drug. The condition constitutes a transient disorder, disappearing when the drug has been eliminated but not yet referable to any arbitrary blood concentration above or below which mental symptoms appear or disappear. Fortunately there seems to be no definite summation of mental symptoms referable to disease plus drug. However, within the realm of cerebration some interesting experimental findings have been recorded concerning the combined effect of the sulfonamides and certain other drugs. Of possible clinical importance are the results reported by Adriani[1] concerning the combined effect of sulfanilamide and some of the anesthetic drugs. The anesthetic action of ether and chloroform was found to be the same in normal animals and in those receiving sulfanilamide. However, when an amount of barbiturates—such as amytal, nembutal and others—necessary to induce anesthesia was administered to rats, if the animals were receiving sulfanilamide, they died, whereas normal controls emerged from the anesthetic state unharmed. Furthermore, an amount of barbiturates which induced only subanesthetic states in normal rats, caused deep anesthesia and in some instances death in animals receiving sulfanilamide. The implications of these findings concerning the selection of the type of anesthetic in surgical patients receiving sulfanilamide are obvious. The question might also be raised concerning the advisability of administering barbiturates for sedative or soporific purposes, although the dosage may be too small to give results comparable to those found in experimental tests with anesthetic doses of barbiturates. Glaubach[2] has reported that the sedative and anesthetic effects of papaverine are augmented by sulfapyridine. When an amount of papaverine, which in normal animals produced a

transient narcotic effect, was given to other animals receiving sulfapyridine deep narcosis resulted and some of the animals died.

These findings indicate that the transient psychic reactions noted clinically, although not serious when taken alone, may have a deeper significance when other drugs affecting the higher centers are given simultaneously.

Nausea and Vomiting

With sulfapyridine therapy, nausea and vomiting are by far the commonest toxic effects. In this respect sulfapyridine differs strikingly from sulfanilamide, and this difference illustrates the unpredictableness of pharmacological effect when chemical structure is altered, although the sulfonamide grouping remains present in both drugs. The incidence of nausea and vomiting, or both, has been noted by observers in frequencies which usually average over 50 per cent. The nauseous and emetic action is currently believed to be of central origin, the chief factor favoring this interpretation being the fact that the symptoms may arise following parenteral administration of sulfapyridine. However, there appears to be no critical level of blood concentration at which nausea is induced. Furthermore many patients have no difficulty with *mal-de-mer* even though the blood concentration is unusually high, and still other patients begin the upset within an hour or two of beginning treatment. It is apparent that there is an individual personal element which is unrelated to an arbitrary physiological reflex set off by a quantitative level of drug. One interesting fact noted by several observers is that the vomiting, if not extreme in degree, may not seriously interfere with the effectiveness of the remedy nor indeed the blood level. If the intact tablets are not ejected very quickly after ingestion, it is surprising how frequently the curative effect and blood concentration are comparable to results noted in patients who do not vomit.

As with the other untoward reactions so far mentioned, no serious results or persistent after-effects of the emetic action have been noted with the exception of those referable to disarrangement of fluids and electrolytes due to vomiting—conditions which are amenable to adjustment by parenteral replacement—and of those referable to the strain on abdominal wounds and surgical incisions in postoperative pneumonia.

In connection with problems in sulfonamide therapy which are of special interest to surgeons, the report of Bricker and Evarts Graham[3]

may be of interest. Using dogs in an experimental study they found that the tensile strength of a recent incision in the wall of the stomach was less in dogs which were receiving sulfanilamide than in normal animals. They noted that this tensile strength of the wound in sulfanilamide treated animals was weakest very early after the repair process began and that the difference between normal and treated animals was less significant the longer after the operation the tests were made. These findings suggest that fibroblasts may be particularly susceptible to impairment by sulfonamides, an untoward reaction which might occur in some other types of embryonal cells, as in the immature cells of the bone marrow.

Hematopoietic System

Of more importance than the transient and almost uniformly harmless toxic manifestation just mentioned, is the damaging effect upon the blood cells and blood-cell-forming organs. This occurrence may assume serious proportions and constitutes the chief cause of fatality following sulfonamide therapy. Among the published reports of cases treated with sulfapyridine, six deaths have been directly attributable to the action of the drug on the blood-forming organs. With sulfanilamide there are a somewhat larger number of reported fatalities. However, in either case, the numbers are very small in proportion to total number of treatments. Non-fatal cases with alterations in blood cells have also been observed of mild, moderate and severe degrees. The granulocytes rather than the lymphocytes suffer the greatest damage. In the fatal cases, the white blood-cell-forming marrow suffers from a damage which is irreversible even though administration of the drug is stopped. When a drop in the number of white blood cells sets in, there is at present no way of determining whether the granulocytopenic effect will cease when therapy is stopped or will proceed to a fatal outcome.

We have had the opportunity to observe in a few instances unusually transient effect of the drugs on white blood cells. One instance will illustrate the point. The patient had gonococcal arthritis and was treated with sulfanilamide. She developed some toxic manifestations and the drug was stopped. At a later date when conditions had reached normal equilibrium, she was given a gram of sulfanilamide and blood counts were done at two-hourly intervals for most of the ensuing twenty-four hours. Her count steadily rose for about fifteen hours until it doubled

itself, then dropped quickly again so that by twenty-four hours it was at the same level as at the beginning. In this case daily determinations of the number of white blood cells after the single dose would have failed to reveal the episode of transient irritation. Findings such as this also suggest that minimal effects may occur more frequently than is ordinarily suspected.

The question of individual idiosyncrasy which this patient also illustrated is an interesting one. The frequency with which the same individual responds with the same toxic reaction has not been settled. That it occurs in some instances is clear. The question may also be posed but not answered, whether individuals who react unfavorably to sulfonamides may have a broad idiosyncrasy to drugs such as amidopyrine and others.

When the red blood-cell system is chiefly affected the manifestations appear as an acute hemolytic anemia, or as a secondary anemia which develops with varying degrees of rapidity and severity. The acute hemolytic phenomenon is characterized by destruction of half or even more of the circulating red blood cells within a day or two. Irritation of white blood-cell-forming organs accompanies the event and is manifested by an unusually high leukocytosis. The hemolytic crisis appears to occur somewhat less frequently with sulfapyridine than with sulfanilamide.

In addition to the acute incident, secondary anemias, which gradually develop over days or weeks, have been noted, in which red blood cells and hemoglobin may drop to varying levels as low as half of normal only to return uneventfully to normal following cessation of the drug.

On the basis of the present limited knowledge, the findings suggest that the toxic effect on the white blood cells is most frequently reflected by damage exerted at the source, namely the bone marrow, where immature early forms of cells are present; whereas with red blood cells the mature circulating forms are particularly vulnerable to destruction.

Urinary Tract

Perhaps the most significant effect of sulfapyridine, which is not shared to the same degree by sulfanilamide, concerns the toxicity manifested by abnormalities in the urinary tract. Clinically, these are hematuria, calculus formation and nephritis.

The rapidity of the renal excretion of sulfanilamide and sulfapyri-

dine is one of the striking characteristics of the drugs. The mode of excretion is also of interest. Marshall and associates[4] have found that they are eliminated by glomerular filtration and that reabsorption to the extent of 80 per cent occurs in the tubules, a procedure similar to that by which urea is handled in the kidney. This indicates that the tissues of the glomeruli and the tubules are exposed to whatever effects the drugs may exert while transferring either from blood to lumen of the tubules or from lumen back to blood.

It has also been made clear that sulfanilamide and to a greater extent sulfapyridine undergo chemical alterations in the body, one of which is acetylation. This particular change in chemical constitution results in a compound which is poorly soluble and therefore crystallizes readily out of solution. It appears, therefore, that the crystalline form is the source of the damage. The crystals in all probability scratch the lining of the tubules, pelvis and ureters as they progress down the urinary tract. The hematuria is therefore in the nature of mechanical trauma rather than a chemically poisonous effect on the renal cells. When the crystals of acetylated compounds accumulate in sufficient numbers, a calculus is formed, which in itself may reach a size sufficiently large to give all the signs and symptoms of renal colic. Finally nephritis with nitrogen retention and renal insufficiency appears also to be based on this mechanical circumstance, with dilated pelvis, damming back of urine, enlargement of kidney and renal insufficiency. The matter may be further complicated by the fact that above the point of stasis infection may be introduced with pyelitis and pyelonephritis developing. Whether or not primary acute glomerular or tubular nephritis occurs, which is dependent upon damage exerted by the drug in its passage from blood to lumen in filtration or from lumen back to blood in reabsorption, has not been clearly determined. Such a possibility is a reasonable one. McLeod[5] has reported two patients who developed renal insufficiency without hematuria and might fall into this category.

The occurrence of hematuria from the standpoint of frequency is difficult to assay from the literature. As was previously brought out, the earliest reports of cases treated with sulfapyridine did not mention hematuria. This finding has been a matter of special interest in recent reports. Such successive increases in per cent occurrences as 2 per cent, 18 per cent and 25 per cent are noted. It occurs in both children and adults. It occurs at times when the urine is alkaline as well as acid, the insolubility

of acetyl sulfapyridine persisting through wide ranges of pH. It clears up in a few days after treatment is stopped, with certain exceptions that will be subsequently mentioned. One point of interest which may be culled from cases cited in several publications is that patients who developed hematuria at the time of the first administration of sulfapyridine have, at a later period when the drug was given again, developed hematuria again. The individuality of the idiosyncrasy appears on occasion to be applicable to the renal toxic effect as well as in the hematopoietic one. The development of calculi is clearly an authentic occurrence, which has been produced experimentally in several different species of animals[6] and has been observed in treated patients both clinically with the signs and symptoms of renal lithiasis[7] and pathologically by the demonstration of the stones with assay of their chemical constitution.

Nephritis with renal insufficiency constitutes the most serious complication of those involving the urinary tract. Fortunately the incidence is small and I have not found reference to a death due to nephritis, per se. However, what the future outcome may be for persons who have once had functional impairment of the kidneys remains to be determined. Indeed, the eventual prognosis is a question which deserves consideration in the cases in which transient hematuria is the only manifestation of damage to the urinary tract.

In the present state of knowledge, it may be stated that the abnormal appearance of red blood cells in the urine in quantities which vary from a few identified microscopically to gross hematuria is a common but transient occurrence, the exact frequency of which has not been established; that crystals of acetyl sulfapyridine may be identified in the urine either chemically or microscopically, or often may be seen with the naked eye as points of light refraction; that when the crystals agglutinate in sufficient numbers, the problem of renal lithiasis is presented; finally, that nephritis with renal insufficiency may develop. Fortunately, from the standpoint of an immediate reaction, the frequency of these effects and their seriousness appear to bear the relation of inverse proportion, hematuria being the mildest and commonest, nephritis being the most serious but considerably less frequent.

The toxic manifestations which have been emphasized in this discussion have been selected topics which are not inclusive because of the limitations of time. Even from those mentioned it is apparent that sulfonamide drugs are not entirely perfect in the job of promoting the

destruction of bacterial cells while leaving the cells of the body completely unaffected. But it is also clear that the life-saving effectiveness of sulfanilamide and sulfapyridine outweigh the immediate toxic reactions.

In considering these drugs, by way of brief recapitulation, two points, among many, may be selected for restatement. First, what is the combined action of the sulfonamides plus other reagents of either chemical or biological origin with respect to augmenting, supplementing, altering, or inactivating effects on the body? That sulfanilamide and sulfapyridine undergo and induce chemical changes in the body is clearly indicated by acetylation, by esterification, by effects on metabolism such as is reflected in the excretion of porphyrin, and by some as yet unexplained reaction involving oxidation-reduction processes, the most striking manifestation of which is the formation of methemoglobin. What other chemical reactions may occur with what other reagents and lead to what other kind of toxic effects are problems which remain to be determined. From a practical current clinical point of view these unknown circumstances emphasize the importance of judiciously considering the selection of accessory drugs that may be given simultaneously with the sulfonamides. A second unsettled point concerns the effects which may become evident a considerable time after the drugs have been given. The most obvious hazard in this respect is the initiation by crystals of acetylated sulfapyridine of calculus formation. It is not unreasonable to consider the possibility that a nucleus might be established around which and on which mineral salts may be gradually deposited over a period of months or years until the disorder of kidney stone becomes established. It is perhaps also important to contemplate what significance may be attached to the transient abnormalities, which are evident during the period of drug administration but which seem to disappear when therapy is stopped. Is there a residue, for example, of renal impairment or bone-marrow impairment which is so minimal as not to be evident when the patient has recovered but which will eventually add up to a sufficient degree to cause some chronic disease, if repeated over a number of years either with repetition of sulfonamide therapy or other therapies which induce similar damages. If the healing of the body cells intoxicated by the drugs is complete, the incident is a closed one. If damage to some of the body cells is permanent, even if minimal, the summation effect of repeated insidious damage may, when

and if it occurs, eventually be a serious matter. Without implying unwarranted concern for remarkable remedies, the problem justifies detailed observations over a period of years before the seeming harmlessness can in all respects be finally appraised.

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HYPERPITUITARISM AND HYPOPITUITARISM*

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INTRODUCTION

THE pituitary gland, in the words of Harvey Cushing,[1] "exercises direct or indirect control over an unsuspected number of biochemical processes of utmost importance to the economy of the body." There are, for this reason, undoubtedly innumerable states, some pathological, others bordering upon the pathological, in which dysfunction of the pituitary gland is involved. However, our present state of knowledge of pituitary dysfunction without demonstrable morphologic changes in the pituitary gland is such that it is dangerous speculation to attempt to ascribe many bizarre conditions, as claimed by uncontrolled and popular endocrinology, to improper secretion of the pituitary gland.

Indeed, there must be a considerable margin of safety in the quantity of functioning glandular tissue of the anterior lobe of the pituitary body since one not infrequently sees patients with partial destruction of this organ by tuberculosis, syphilis or embolic phenomena without any detectable symptoms ascribable to loss of pituitary secretion.

However, sufficient experimental data and clinical and pathological evidence exist to make possible the recognition of two important classes of pituitary disturbances, namely, hyperactivity and hypofunction of this gland.

Of all the verified diseases of the pituitary gland producing one or the other of these groups of symptoms, the commonest is the adenomatous tumor.[2] The type of clinical response to such a tumor varies with the type of cell from which the tumor arises.

HYPERPITUITARISM

ACROMEGALY

Definition: Acromegaly is a disease which is characterized by a specific type of pituitary adenoma and an overgrowth of the terminal, thus acral, parts of the skeleton such as the nose, mandible, hands and feet.

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History: Pierre Marie,[3] in 1886, is generally accredited with having described this disease. Certainly he gave it its name and presented the first clinical picture of it as a disease entity by the report of two cases. The etiology of the disease was, however, very much in doubt for another fourteen years.[4] The pituitary gland was somehow believed to be involved, but Marie himself thought for a long time that the disease was an expression of underfunction or at least dysfunction of the gland. In 1900, Benda[5] conclusively demonstrated that the pituitary lesion with which acromegaly was associated was an adenoma consisting of cells containing eosinophilic granules, that these granule-bearing cells were similar to those which are present in large numbers during the growth period in normal individuals and that acromegaly was in all probability a result of hyperactivity of the pituitary gland.

In 1909, Cushing[6] was able to demonstrate experimentally that pituitary extirpation retarded skeletal development, and thus inferred that the skeletal hyperplasia, occurring in acromegaly and the related condition, gigantism, was due to hyperactivity of the gland. H. M. Evans[7] (1923) was able to produce gigantism in rats by repeated injections of extracts from the anterior lobes of beef pituitaries; and Putnam[8] (1928), experimental acromegaly in dogs by a similar method.

Etiology: Acromegaly is a rare disease. There are five times as many cases of pituitary tumors of the chromophobe type without acromegaly as chromophile tumors with it. It can occur in all races, and affects both sexes about equally. The disease has its onset at a relatively early age (average about 26 years) but because of its chronic character patients are often first observed past middle life.

Frequently acromegalic patients give a history of notably large kinsmen, and occasionally even of acromegaly in a near relative, but the disease cannot be considered primarily as a familial one.

Morbid Anatomy: The primary lesion in acromegaly is an adenoma of the anterior lobe of the pituitary body consisting of cells, the cytoplasm of which contains granules staining specifically with eosin and other acid dyes.[9] This lesion not only results in an enlargement and deformity of the pituitary gland and consequently of the sella turcica, but because of its oversecretion of hormone, resembling most perhaps the growth-promoting hormone, it produces secondary effects upon practically every tissue and organ in the body.[10] These secondary effects may be divided into two groups, namely, those exerted upon the neighboring

structures of the tumor by the mechanical pressure of the growth, and those exerted upon distant structures by the hormonal influence of its secretions.

The first results in atrophy and enlargement of the sella turcica; pressure atrophy of the optic nerves and chiasm; irritation or atrophy of the hypothalamic portion of the floor of the third cerebral ventricle; occasionally, atrophy of some degree of the olfactory tracts and nerves.

The most conspicuous hormonal effect of the lesion is upon the skeleton. When the onset of the disease is early in life before the closure of the epiphyses, the stature of the patient may increase to gigantic proportions. Authenticated cases of patients attaining a height of eight feet (240 cm.) exist in the literature. These patients, although large, may be symmetrically developed without deformities and are said to suffer from gigantism rather than acromegaly. Most frequently, however, the giants show, in addition to their great height, an undershot jaw (prognathism) and great hands and feet out of all proportion even to their own unusual size, thus approximating the usual type of acromegaly. In addition to the prognathic jaw, the head also shows as a rule a great thickening of the calvarium and an enlargement of the air sinuses. The vertebral bodies and the points of attachment of the muscles and tendons to the bones frequently show marked hyperostoses. The spinal column often shows a fairly marked general kyphosis; the ribs become heavy and the chest cage resembles a great barrel.

In addition to the bone-changes, the nerves, blood vessels, skin, glands, and fat reveal generalized hypertrophy, but this is particularly true of the connective tissue throughout the body. While much of this hypertrophy is due to actual increase in the number of cells and the quantity of intercellular substance, a certain amount is also ascribable to a peculiar edema of the subcutaneous tissues which is moderately mobile and is the first to disappear if the secretion of the adenoma can be diminished by surgical or roentgenologic means.

Less obvious than the enlarged acral portions but equally striking is the generalized splanchnomegaly occurring in this disease. This affects not only the viscera but, to a special degree and in a special sense, the other endocrine organs such as the thyroid, thymus, parathyroids and adrenal glands which are often the seat of adenomatous lesions, so that this disease is sometimes referred to as multiple adenomatosis.

Symptoms: The distinction between symptoms and signs in acrome-

TABLE I

SYMPTOMS AND SIGNS OF ACROMEGALY AS RECORDED IN CLINICAL HISTORIES

Symptoms and Signs	*Incidence (Per Cent)*
Enlargement of acral parts	100
Enlargement of sella turcica on x-ray examination	93
Disturbances of menstrual cycle	87
Headache	87
Complete amenorrhea	73
Increased basal metabolic rate	70
Visual disturbances	62
Excessive perspiration	60
Hypertrichosis	53
Cutaneous pigmentation	46
Drowsiness and lethargy	42
Gain in weight	39
Diminished libido sexualis	38
Asthenia	33
Low blood pressure (less than 120 mm. Hg. systolic)	30
Paresthesia	30
Polyphagia	28
Fibromata mollusca of skin	27
Polydipsia	25
Enlarged thyroid gland	25
Glycosuria (diabetes mellitus 12)	25
Constipation	25
Vomiting	16
Rhinorrhea	15
Photophobia	12
Uncinate attacks	7
Failing memory	7
Decrease of body hair	7
Persistent lactation	4
Failure of breasts to develop	4
Epistaxis	3
Choked discs	3

galy is particularly difficult since many elements belong to both categories. The disease, as may already be suspected from the description of the varied pathological manifestations, is extremely protean[11] and the enumeration of the symptoms and signs in Table I makes a formidable list.

Time will not permit me to discuss more than a few of these in detail:

Acral Overgrowth: The peculiar overgrowth of the hands, feet and features is of necessity present to some extent in every case, since the clinical diagnosis and the name of the disease is based on the presence of these manifestations. A closer investigation of the acromegalic patient reveals that the overgrowth is general and not confined to the extremi-

ties. The changes in the latter, however, call attention to the disease. The hands and feet become much enlarged, but especially in width and thickness and the first inkling of this change may come to the sufferer through the need of frequently increasing the size of his gloves and shoes. The skin becomes thickened and the joints of the fingers and toes become relaxed; the pores are coarsened and perspiration increases so that one gains the impression in grasping the hand of an acromegalic that it consists of a moist, relaxed sac incompletely filled with loose bones. The nose becomes wide and large; the lips and brows thicken; the spaces between the teeth increase, owing to the enlargement of the jaws, and the lower jaw becomes prognathic because of its relatively even greater hypertrophy than its fellow. The tongue hypertrophies so that it overfills the cavernous mouth and the speech grows lisping and indistinct.

If the onset of the disease occurs before the closure of the epiphyses, the entire stature increases beyond normal and may reach gigantic proportions. The circumference of the chest becomes greatly augmented. Sooner or later a "rounding" of the shoulders occurs due to hypertrophic changes in the vertebrae.

Menstrual Changes: In the majority of female patients, oligomenorrhea or amenorrhea appears early in the disease. This symptom is associated with sterility since impregnation in an acromegalic woman practically never occurs after the onset of amenorrhea, although acromegalic women can bear children if their menses continue. The interruption of ovarian function seems at first incompatible with the fact that in cases of chromophobe adenoma of the anterior lobe of the pituitary, which present in every other respect a directly antithetical picture, amenorrhea and sterility are also produced. Henderson[12] has shown, however, that the onset of this symptom in either type of adenoma is related to the size of the tumor, and comes about when this has attained such a size as to interfere with the sex stimulating hormone of the normal part of the anterior lobe.

Headache is present in nearly 90 per cent of acromegalic patients who apply for treatment to the neurologist and more especially neurological surgeon. This symptom is due, it is believed, to the stretch put upon the dural diaphragm across the sella turcica by the expanding tumor within it.

Visual Disturbances: These consist of symmetrically disposed visual field defects in the temporal halves of the fields which progress until the

typical bitemporal hemianopia is produced, and which, if untreated, may go on to complete loss of vision. The cause of these changes is the pressure of the tumescent gland against the optic chiasm. If the tumor is allowed to grow beyond this point, it may break through its capsule and extend into the cranial cavity. When this occurs, the growth is usually asymmetrical and the visual field defect may change correspondingly. Rarely one even sees papilledema with a pituitary adenoma as a result of intracranial extension and increased intracranial pressure. The usual picture of the eyegrounds is one of primary atrophy of the optic discs.

Complications: The complications in the course of this disease are practically all due to the advancement of the above symptoms to their final stages:

Blindness may result if the growth of the adenoma continues and is not checked either by operation or roentgenotherapy.

Increased intracranial pressure may occur if the tumor breaks through the confines of its capsule and all its accompanying symptoms may appear.

Diabetes mellitus is a common complication, and though it does not run a course similar to the essential type of diabetes, nevertheless, it may end in diabetic coma.

Increased basal metabolic rate is frequent in acromegaly and sometimes this reaches a state analogous to thyroid toxicosis. Resection of the thyroid usually improves this condition, although histologically the thyroid shows the picture of a colloid goiter instead of that of hyperthyroidism.

Asthenia and low blood pressure may occur.

Arteriosclerosis and myocarditis are more common and occur at an earlier age than would be expected in normal individuals.

Diagnosis: The diagnosis of acromegaly (pituitary acidophilism) is the simplest thing about the disease. The coarse features and especially the prognathic jaw, the huge hands and sausage-like fingers, the great feet, barrel chest, rounded shoulders and ape-like carriage, make the diagnosis possible literally at a distance. When the disease begins very early in life, however, the stature may be abnormally great but the acral portions, though large, are as a rule more shapely, and in proportion to the rest of the body. While severe acromegaly can exist with an adenoma so small that the sella turcica is not expanded, in the majority of cases the tumor enlarges the gland enough to give some visual field defects

and changes in the sella turcica sufficient to be visible in roentgenograms of the skull.

The Roentgen films of the skull in acromegaly characteristically show thickening of the calvarium, ballooning out of the frontal sinuses, prognathism and a sella turcica which is enlarged to greater or less degree, often with depression of the sellar floor and thinning or erosion or even complete destruction of the anterior and posterior clinoid processes and the dorsum sellae. The terminal phalanges of the fingers and toes show a peculiar "tufting" on the roentgenogram, which is quite characteristic of the disease, and the rest of the skeleton presents a massiveness which is easily recognizable.

Prognosis: Acromegaly is a chronic disease which may last as many as forty years in an attenuated form. Often the adenoma degenerates or loses its secretory qualities and the patient may go into a state of hypopituitarism due not only to a "burning out" of the adenoma but also to the destruction of the normal pituitary gland. However, whether sufficient of the normal pituitary gland remains or not, and even when the adenoma ceases functioning altogether, the skeletal changes do not recede, so that the patient's appearance is always that of an acromegalic. Frequently the growth of the adenoma and its secretory capacity continue unabated and unless treated, produce blindness, intolerable headaches, and the various other complications until death ensues.

Treatment: Since the basic pathological lesion in acromegaly is the acidophilic adenoma of the pituitary gland, treatment, in order to be fundamental, must be applied directly to this growth. This may be done either by surgical or roentgenological methods or a combination of both. The acidophilic adenoma of acromegaly is radiosensitive in about 60 to 70 per cent of cases. If the patient presents himself sufficiently early, before his visual power is threatened, radiotherapy should be tried. If the vision is in imminent danger, a partial surgical extirpation of the tumor should be made and roentgenotherapy applied postoperatively to devitalize the remainder of the growth.

The most modern surgical procedure consists of a right transfrontal craniotomy, carried out under local anesthesia with an attack upon the tumor between the legs of the optic chiasm, through the bulging sellar dural diaphragm, which has first been incised.

The Roentgen-ray treatment is delivered through three portals, one on each temple and one in the midfrontal region, of 5 x 5 cm. Through

each of these portals, 800 r units are delivered in divided doses of 200 to 300 r units per treatment given daily or every other day. The physical factors in the set-up depend, of course, on the facilities available. As a working method, the following factors may be used:

Kilovolts	200
Milliamperes	8
Screening	(1 mm. Al. (0.5 mm. Cu.
Distance (target to skin)	50 cm
r per minute	20

Pituitary Basophilism

Definition: Pituitary basophilism is a condition chiefly affecting women, and associated with an adenoma of the anterior lobe of the pituitary gland consisting of cells with basophilic granules in their cytoplasm. This point is still controversial and may have to include certain cases without adenomas but in which the basophilic cells of the anterior lobe show certain hyaline changes first described by Crooke in 1935. Clinically it presents a syndrome of painful obesity, hypertrichosis, amenorrhea, with overdevelopment of secondary sex characteristics, plethora, vascular hypertension, purplish striae of the skin, osteomalacia, and a number of other more variable signs and symptoms.

History: In 1903, Erdheim described the postmortem findings in two cases which showed, on careful histological examination of the pituitary, small adenomas 1.5 mm. and 1 mm. in diameter respectively, consisting of basophilic granule-bearing cells. He considered these incidental findings, in the nature of histological curiosities, and placed no clinical significance upon them. One of these patients, during life, was considered to be suffering from Basedow's disease, and the other was an acromegalic who showed a large acidophilic adenoma of the pituitary in addition to the tiny basophilic one.

In 1912, in his well-known monograph on "The Pituitary Body and Its Disorders," Harvey Cushing[1] described a "polyglandular" syndrome, in a young woman of twenty-three, which he defined as "a syndrome of painful obesity, hypertrichosis and amenorrhea with overdevelopment of secondary sex characteristics," without being able to attribute the picture primarily to the pituitary, adrenal, pineal or ovary. This patient was seen by him from time to time for over twenty years.

Meanwhile six other similar cases appeared under his observation, and a number of these "polyglandular" cases began to appear in the literature, a few of which were reported together with complete postmortem examinations. One of the most complete reports was by Parkes Weber[13] (1926) in whose patient, among other pathological changes, was found a small pituitary basophilic adenoma to which he ascribed very little significance. Meanwhile, biological evidence of multiple hormones of the anterior pituitary gland was being disclosed and a young co-worker of Cushing, Harold Teel[14] (1931), postulated the presence of a basophilic adenoma in an obese, hirsute woman who also showed menstrual irregularities, and at whose necropsy such a lesion was found.

A search of the literature revealed a number of similar cases, some of which occurred also in males, and in 1932, Cushing's paper[15] appeared with a full review of all reported cases and a number of his own. One of these was that of a man who showed this syndrome to an advanced degree, and in whom a basophilic adenoma of the pituitary was postulated. He improved remarkably after radiation therapy confined to the pituitary region. This seemed to indicate that the lesion primarily responsible was located in the pituitary gland. What that lesion was, as yet was not verified. Later on, however, the patient had a recurrence of symptoms and died before he could be brought back to Cushing's care. Necropsy revealed the presence of a basophilic adenoma of the pituitary gland and the last link in the chain seemed to have been forged to establish the syndrome of pituitary basophilism.

Morbid anatomy: Most of the postmortem examinations in those examples of this disease which are recorded in the literature were made before Cushing linked the syndrome to the basophilic adenoma of the pituitary gland. Since this tumor is usually small, often no more than a few millimeters in diameter, it undoubtedly was occasionally overlooked when no special effort was made to find it. As an example, a case reported by Bauer[16] was examined at necropsy by Sternberg, whose report of the pituitary gland was that it was of normal size without change. After the case was published, at the request of Cushing, Sternberg cut the pituitary gland serially and found a small, but typical, papillary basophilic adenoma. It is this lesion, then, which is believed to be the basically underlying pathological cause for the disease.

The other members of the endocrine series are also involved to a greater or less degree. The adrenals often show adenomatous formations

or hyperplasia of the cortex, although normal adrenals have been described in typical examples of the disease. The thyroid is usually normal in size or slightly enlarged. Occasionally a small struma may be present which histologically proves to be colloidal in character. The thymus has usually been reported as atrophied although, in Teel's case, it was found to be persistent. No uniform changes have been seen in the pancreas or pineal. From the few reports on the condition of the parathyroids, it would seem that these bodies are hypoplastic in this disease. The gonads are usually atrophic.

The other tissues and organs show varying degrees of change. The blood vessels are often sclerotic, in spite of the relative youthfulness of the subjects. The heart, as a rule, shows considerable hypertrophy, not in the massive sense as seen in acromegaly, but compatible with a state of chronic hypertension. The kidneys almost consistently show chronic nephritis. The liver may show fatty degeneration, although no detailed studies are reported in the literature.

Symptoms: Until many more case reports appear, now that the nature of the disease is better known, the complete clinical picture will have to remain uncertain. In many of the case reports that are extant, the histories are often very much condensed and the chronological appearance of symptoms incompletely noted. In so far as it is possible to determine, the cessation of menses is usually the first symptom in women, unless the disease appears before puberty. In the male patients, obesity is the first indication of the disease. Headache is common; pain is frequently present, especially in the back. The women note, fairly early in the disease, a thinning of the hair on the head and the appearance of body and facial hirsutes. Shortness of breath and palpitation, general weakness, purpuric eruptions are frequently reported. Loss of height, associated with cervicothoracic kyphosis, was observed subjectively in five out of sixteen cases analyzed. Less frequently, exophthalmos, diplopia, nausea, vomiting, epistaxis, tinnitus, dry skin, insomnia or somnolence is noted by the patients.

Objectively the appearance of these patients is as striking in its way as that of the acromegalics. The female victims show a definite growth of hair on the face, although the hair on the head may become thinned. All the patients have strikingly prominent abdomens, suggesting in appearance that of the later months of pregnancy. The obesity extends to the rest of the torso, breasts, neck and jowls. The skin is often

stretched very tightly over these localized areas of obesity and gives the patient a painful feeling as if it were about to burst. On palpation, too, the fat pads are often tender. Contrasted to the obese body and neck, the extremities are usually thin, even wasted. The face is plethoric; the eyes may be prominent and the conjunctivae injected. Purpuric spots are frequently present. Owing to the stretching of the skin, striae are usually present and characteristically appear purple, red or brown. These may be very prominent over the abdomen, thighs, breasts and even axillae. The skin, in addition, may be quite dry and scaly and often shows brown pigmentation in the folds of the body.

The patient usually shows a fairly marked cervicothoracic kyphosis which accounts for the loss of height of which he may complain. The Roentgen-ray examination of the spine in these cases shows a marked porosity of the bone due to the loss of calcium and a wedging of the bodies of the vertebrae in the kyphotic region. X-ray examination of the other bones also frequently reveals porosity. The skull, too, is usually involved, and the sella turcica, while seldom enlarged, shows thinning of the clinoid processes, floor and dorsum sellae, not often as a result of local pressure, but as a part of the general process.

The blood pressure, both systolic and diastolic, is almost invariably high and the fundi oculi frequently reflect this state in the form of retinal hemorrhages, exudate, tortuosity and sclerosis of the blood vessels.

Occasionally there is a distinct, though not very marked, polycythemia with a red blood cell count of five and one-half to six and one-half million. In about a third of the patients, hyperglycemia and glycosuria are present.

The basal metabolic rate has been measured in a few of the cases reported and was found to vary between −33 and +33, although the tendency is for it to be somewhat above the normal.

Complications: The influence of the abnormal secretions of the basophilic adenoma may result in numerous complications associated with hypertension (e.g., cerebral hemorrhage, chronic nephritis, retinal hemorrhages); with decalcified bones (e.g., spontaneous fractures, kyphosis); with glycosuria (e.g., a tendency to acquire infections, even diabetic coma).

Diagnosis: The striking clinical picture makes the diagnosis of the syndrome extremely easy. The only difficulty is that known cases of

apparently the same disease have been found which were believed due to tumors arising from the adrenal glands, and in whom no tumor of the pituitary gland was said to exist. Since it is known that the pituitary adenomas are often very small, the failure to find them in the past is not completely acceptable evidence of their absence. In relation to this condition, the student is witnessing a chapter of medical history in the making. Harvey Cushing has built up his evidence like a true veteran with full awareness of all the pitfalls that await the explorer in a new field. For lack of material, however, some of the facts still need confirmation.

Prognosis: Pituitary basophilism is a chronic disease; the average patient presents himself for hospital study more than seven years after the onset of the first symptom. Dr. Cushing followed his first case for over twenty years after he first saw her. Death usually results from some intercurrent disease, or one of the complications mentioned above. The disease has been known to become arrested spontaneously. Some hope exists that improvement may be brought about by treatment of the primary tumor of the pituitary gland either directly by surgery or indirectly by the Roentgen ray.

Treatment: Following the analogy of the other adenomas of the hypophysis, the treatment which immediately suggests itself is either extirpation of the tumor by surgical means, or its devitalization by roentgenotherapy, or both. So far, I know of no case that has been successfully operated upon. Several patients, however, have shown remarkable improvement following radiation directed to the region of the pituitary body.

Hypopituitarism

Definition: Hypopituitarism is a condition resulting from interference with secretion of the pituitary body either by tumor, degeneration or infection of the gland. The effects vary with the degree of functional disturbance of the pituitary and its neural connections with the hypothalamic portion of the brain, as well as with the age of the patient at the time of onset of the disease.

History: The association of pituitary tumor with blindness has been recognized since 1705 when Vieussens[17] reported the case of "le cardinal de Bonsy" who showed at necropsy a pituitary tumor the size of a hen's egg. From that time a relatively large number of cases were reported,

showing disturbance of vision with such tumors. The first known case in which obesity was linked with the combination of pituitary tumor and visual disturbances was reported by Mohr[18] in 1840. It was not, however, until after acromegaly was described in 1886 and the symptoms of this disease linked with a tumor of the pituitary gland that the constitutional changes in patients harboring a pituitary tumor were carefully scrutinized. The demonstration of pituitary tumors in the absence of acromegaly was considered proof against the assumption that the acromegalic symptoms were a result of the tumor. The recognition that there was a difference in the character of tumors primarily originating in the pituitary gland did not come until 1900 when Benda[5] produced incontrovertible microscopic proof of this contention. In 1901, Froehlich[19] described the case of a 14-year-old boy with headache, vomiting and obesity, underdeveloped genitalia and absent pubic and axillary hair, who harbored a tumor in the region of the pituitary gland. To this syndrome, Bartels[20] later gave the name of "dystrophia adiposogenitalis." This was considered a prototype of hypopituitarism until Philip Smith[21] showed by his experiments with rats that, in all likelihood, the so-called pituitary obesity was probably not a result of direct disturbance of the pituitary gland but rather of the neighboring hypothalamic portion of the brain. By his experiments, the distinction between a lesion of the neighboring brain and of the pituitary body was first made. Previous experiments were inconclusive since, as a rule, in an attempt to produce the one lesion, the other was also inadvertently made. In the experiments which he carried out to show the effect of ablation of the anterior lobe of the pituitary gland without injury to the brain, he was able to demonstrate that in immature individuals growth ceases; sexual development fails to take place; but obesity does not occur. In adults who have attained their full growth, very little effect is noted aside from dystrophy of the gonads and a thinning and falling out of the hair.

Chromophobe Pituitary Adenoma

The commonest cause for hypopituitarism is the chromophobe adenomatous tumor of the anterior lobe of the pituitary gland, which has no known secretion of its own, and which compresses and interferes with the function of the normal pituitary body.

Etiology: These tumors are by far the commonest variety affecting the pituitary gland, making up about two-thirds of all the adenoma cases.

It is a disease of adult life, being fairly evenly distributed in the third, fourth and fifth decades at the time when the patients seek aid in a hospital.

Morbid anatomy: This tumor is usually soft, brownish red in appearance, with a fibrous capsule of varying thickness. It is composed of very thick columns of cells separated by septa of connective tissue carrying delicate capillaries. The cells are elongated, columnar, and often stand at right angles to the connective tissue septa. They have rather indistinct boundaries and their pale staining cytoplasm contains no granules other than mitochondria. The nuclei are small, oval with heavy chromatin material.

The other members of the endocrine series, especially the thyroid, adrenals and gonads, as well as the other organs of the body, are likely to be smaller than normal, in contrast to the condition seen in acromegaly.

Symptoms: The chromophobe adenomas are again large tumors and produce, as a result of local pressure, headache, primary optic atrophy, bitemporal hemianopia, and roentgenographic evidence of enlargement, atrophy, often indeed, complete destruction of the sella turcica. If the growth continues to expand, pressure upon the oculomotor, trochlear and abducens nerves may result in strabismus, ptosis and pupillary changes. At times, the olfactory tracts may be compressed with resulting unilateral or bilateral anosmia.[22] Extension of the tumor outside of the confines of the enlarged sella turcica may result in pressure upon the hypothalamus causing at times polyuria and polydipsia (diabetes insipidus); or if it extends laterally and compresses the uncinate region, may cause hallucinations of smell. In rare instances, these tumors grow so large that they extend up far enough to obstruct the foramen of Monro, which prevents egress of fluid from the lateral ventricles, thus producing an obstructive hydrocephalus with all the signs of increased intracranial pressure.

Just as constant as the local pressure signs above described, are the constitutional changes accompanying this tumor. Usually the first of these symptoms to appear and the most constant is amenorrhea, or, in the male, loss of sexual libido and eventually also of potency. Next in frequency are atrophic changes of the skin, thinness and dryness of the hair on the head, loss of body hair, scantiness of axillary and pubic hair, the latter even in males, being feminine in distribution. About 80 per cent

of the patients show an abnormal degree of obesity which is characterized by a fluctuation in body weight, so that a gain or loss of 10 to 15 kilograms in a year is not unusual. The basal metabolic rate in these patients is usually low, the average being around 20 per cent below normal. This may be responsible for the sluggishness of these patients, their slow pulse and occasionally subnormal temperature. Since the disease has its onset, as a rule, after adolescence, infantilism is seldom seen accompanying it, although the size of the male genitalia is frequently within the lower ranges of normal.

Diagnosis: Since tumors causing hyperpituitarism are easily diagnosed by the constitutional changes they produce, the differentiation of chromophobe adenomas from them is relatively easy. Difficulties may arise, however, in distinguishing the chromophobe adenoma from other tumors in the region of the sella turcica, such as craniopharyngioma (bucconeural tumor), suprasellar meningioma, glioma of the optic chiasm, aneurysm of the circle of Willis, chordoma, angioma, cholesteatoma, tuberculoma or gumma. Some of these conditions resemble clinically the chromophobe adenoma by producing similar focal symptoms; others reproduce the endocrinological changes; while some produce both. Differentiation, however, can usually be made by considering the history, Roentgen-ray and encephalographic data.

Prognosis: Chromophobe adenoma of the pituitary gland is a more rapidly progressive disease than the eosinophilic tumor of acromegaly. It seldom lasts over ten or fifteen years, and frequently, even in spite of treatment, leads to blindness, headache, paralyses resulting from intracranial extension of the tumor. Anemia, asthenia and intercurrent infection frequently are seen in the terminal stages of the disease.

Treatment: Treatment is again either surgical, roentgenological, or both. The results of neither, nor both in combination, are as good as in acromegaly. The techniques employed are about the same as in acromegaly.

Simmonds' Disease[23]

A very extensive, at times even complete, degeneration of the pituitary gland sometimes occurs. This may come about as a result of trauma, infarction or infection of the gland. It produces a rapidly fatal, progressive disorder described as hypophysial cachexia. The patient becomes rapidly emaciated and extremely weak. He seems to age very quickly and usually dies of some intercurrent infection. Recent reports

in the literature of improvement in examples of this disease, as a result of parenteral administration of anterior pituitary hormones, have appeared. Reliably potent preparations of these hormones are not yet available commercially and this treatment is still experimental.

In the diagnosis of this disease special care should be taken to differentiate it from anorexia nervosa which Sir William Gull described 70 years ago. This superficially presents a similar picture but is actually a functional disease based upon psychological maladjustment and is amenable to psychotherapy.

Dwarfism

Aside from the failure of development in stature resulting from congenital abnormalities like achondroplasia, states of malnutrition and insufficient vitamins, many of the pathologically small statures are probably related to dysfunction of the pituitary gland. In some of these conditions, gross abnormality of this gland can be demonstrated. In others, this does not always seem to be the case.

Hypophysial infantilism: One form of dwarfism in which a lesion of the pituitary is usually demonstrable is known as the Levi-Lorain type. This condition is often the result of infarction of the glandular portion of the pituitary, occurring during some acute infectious disease of childhood with a resulting disturbance probably of both the growth and sex factors of the pituitary hormone. The patients usually tend to retain their childish proportions. Their bones are of light construction; the skin is delicate; the primary sex organs never develop beyond the state of childhood, and secondary sex characteristics do not make their appearance. These patients are usually normal intellectually, indeed, are sometimes exceptionally bright. They maintain fairly normal health and make up a fairly large proportion of the dwarf colony in circuses. They seem, however, to have relatively poor resistance to infection and usually die relatively young of some infectious disease. Occasionally this type of dwarfism is accompanied by mental deficiency.

Primordial dwarf: In contrast to the childlike proportions of the Levi-Lorain dwarf, the primordial dwarf, whose stature is frequently below that of the former, nevertheless, develops the proportions of an adult. These individuals appear as miniature men and women; their sexual function is normal; ossification of the skeleton takes place at the normal age. The condition is hereditary and is transmitted through the

father. The famous general, Tom Thumb, and his family were examples of this condition. The pituitary gland, although small, so far as is known shows no gross abnormalities.

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HYPERTENSION—THE PROBLEM, THE STUDY, THE FUTURE*

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THE aeroplane glides through the sky billowed up by the pressure of air beneath its wings. The streamlined locomotive rushes across the continent powered by Diesel engines. This engine turns because heat is generated by compression of the gases, thus causing combustion of the fuel. An electric motor spins due to the reaction of the magnetic fields created around the coils of wire in its revolving parts. Hypertension is caused by a spasm of the smaller blood vessels throughout the body.

Each of these above statements are facts. Merely repeating them, without further elaboration, does not necessarily show a very profound understanding of the details or the ground work of knowledge necessary to evolve them. When a breakdown comes, one needs more working knowledge than general facts to remedy the difficulty. In the case of hypertension, have we not been concerned with the end-result, "the tension," found in the blood vascular system of the patient said to have high blood pressure? Our attention being focused on this fact, it is agreed that the arterial spasm must be relieved to prevent disaster. Treatment by medication has been the method at hand. It has long been directed in a pseudo-magic attempt to lower that tension. The clinician had little time except to try the various drugs on his willing patients. This method of "pouring oil" on the "troubled waters" is not the mechanic's method of attacking his problem. He seeks out the faulty part of the motor and treats it. He knows the result or dysfunction of the engine is due to a worn or broken part. The satisfactory performance will come when the defect is remedied.

THE PROBLEM

In studying the basic facts of hypertension, the mechanic's procedure has been used, but the answer has been slow in evolving. It began a

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century ago, when Bright[1] called attention to the kidney in a patient dying with hypertension. This finding became so common that the kidney was agreed upon as the cause and the disease affecting it bore Bright's name. Gull and Sutton later noted that the disease was not confined to the kidney but all the smaller vessels throughout the body were involved. It followed from this observation that hypertension was regarded as a generalized vascular disease with the kidney only a small part of the process. No matter what view one takes as to the cat and the tail of this controversy, the real problem in understanding hypertension has to do with the character of the agent raising the arterial pressure. Not until we fully understand this, can any question be settled finally or satisfactorily. It is agreed there is more or less uniform narrowing of the small arteries and arterioles. There are three ways in which this narrowing might occur, namely, from a morphologic change in the vessels themselves; from a vasoconstriction of nervous origin; or from a stimulation of the vessel walls by chemical elements in the circulating blood.

It is generally accepted from the histologist's point of view, that the arterial narrowing morphologically is a fatty hyalin thickening of the intima and a hypertrophy of the media.[2] General agreement has it that the intimal change per se is insufficiently widely distributed to cause a rise of tension. On the other hand, the tendency for the peripheral arteries to show marked changes secondary to heat and cold stimulation leads us to believe that this thickening is a work hypertrophy similar to that observed in cardiac musculature.[3,4,5,6,7]

Those sponsoring the nervous hypothesis do not clearly state the way overactivity of the vasomotor nerves is brought about. They rely mainly on the evidence derived from the "cold pressor test" and from the effects noted in dividing the sympathetic supply to the abdominal viscera. On the other hand, Pickering and Kissin[8] have shown that the cold pressor test with a marked response to cold is not peculiar to essential hypertension. It is found in many normal individuals. So that this test cannot be considered as the last word in drawing the conclusion that there is an overactivity of the nervous mechanism to the arterioles. The operations for denervating the splanchnic area are of two kinds: section of the anterior spinal roots from about the sixth thoracic to the second lumbar, and section of the major and minor splanchnic nerves above or below the diaphragm with removal of the adjacent sympathetic ganglia. These two operations seem to produce similar effects on

arterial blood pressure in essential hypertension.[9,10,11] In some patients the fall of blood pressure is profound and persistent. In most cases a considerable fall is ultimately followed by a return to approximately the preoperative level; and in a few the blood pressure is unaltered.

The Study (Experimental)

The study concerns the last possibility, that of a chemical substance present in the blood. What work has been done regarding this? Where does it lead us? What are the inferences from the results? Animal experiments show that arterial tension is increased by procedures that decrease the blood flow through the kidney. These procedures have been varied in method but the results are the same. They are:

1) Excision of varying amounts of renal tissue.
2) Constriction of the renal veins.[12,13]
3) Production of an interstitial fibrosis of the kidney by exposure to x-rays.[14]
4) Ligation of one or both ureters.[15,16,17]
5) Partial ligation of the renal arteries.[16,17,18,19]
6) Compression of the renal arteries with adjustable clamps.[20,21,22]

Most significant and instructive seems to be the compression method of Goldblatt and others in which renal ischemia is produced by adjustable silver clamps. On the other hand constriction of equally important blood vessels, as the superior mesenteric artery, does not cause elevation of blood pressure. Therefore, we are led to believe it is not constriction of the blood supply to any organ that gives this result, but a specific organ, the kidney. However this work was open to criticism. It required further proof to convince investigators that the application of clamps to the arteries did not cause reflex spasm. This type of hypertension was not prevented or relieved by:

1) Denervation of the kidney pedicle.[23,24,25]
2) Excision of the splanchnic nerves.[26]
3) Complete sympathectomy.[27]
4) Complete destruction of the spinal cord.[24,28,29,30]

Therefore a chemical substance was presumed to come from the ischemic kidney, acting on the blood vessels themselves or through the vasoconstrictor nerve-ends. This is borne out partially by the following:

1) A "pressor" substance can be found in extracts of normal kidneys.[31]

2) Much more of this "pressor" substance is found in extracts from diseased kidneys.[32]
3) Excision of the experimental ischemic kidney at the height of the hypertension it produces, allows a prompt return of the blood pressure to normal.[21,33]
4) Transplantation of the ischemic kidney from the loin of one dog to the groin or neck of another produces the same result in the second experimental animal.[34,35,36]

TABLE I

INTERFERENCE WITH RENAL CIRCULATION

This is accomplished clinically by:

I. *Intrinsic,* infection within the kidney—

Bilateral resulting from	Benign prostatic obstruction		
	Partial occlusion of ureters		
	Accompanying bladder	stone, diverticula, malignancies	causing clinical pyelonephritis
	Bilateral infection		
Unilateral resulting from	Pyelonephritis		
	Calculi		
	Contracted kidney	from infection, from trauma	
	Tuberculosis of kidney		

II. *Extrinsic,* effecting interference on the renal artery circulation

Unilateral	Malposition of the kidney
	Abnormal course and position of artery
	Hydronephrosis with pressure on artery
	Atheromatous plaques
	Infarct of kidney
	Thrombosis with recanalization

Examples

I. *Intrinsic,* infection within the kidney:

Bilateral:

1. Cohnheim[37] as far back as 1877 reported cardiac hypertrophy presumably from hypertension with urinary obstruction and a large stone in the bladder.
2. Pässler,[38] 1906, reports a case of anuria of 12 days duration due to a carcinoma of the cervix partially obstructing both ureters, accompanied by hypertension.
3. Longcope and McClintock[39] in 1910 called attention to the clinical relationship of chronic pyelonephritis and hypertension.
4. Brasch[40] in 1911 reported three cases of genital carcinoma with urinary obstruction and elevated blood pressure readings.
5. von Monakow and Mayer[41] in 1918 reported cases of prostatic hypertrophy with reduction of elevated pressures following bladder drainage.
6. O'Connor,[42] 1920, and again in 1923 noted a fall of blood pressure in seventy-four cases of bladder neck obstruction following satisfactory bladder drainage.
7. Staemmler,[43] in 1932, collected thirty cases of pyelonephritis with contracted kidneys and marked elevation of blood pressure and cardiac hypertrophy.
8. Fishberg[4] in 1934 commented on several cases of hypertension associated with urologic disease.
9. Ritch,[44] 1936, reported the benefits of urologic treatments in six cases of hypertension.
10. Longcope[45] more recently reported hypertension in 50 per cent of his twenty-two cases of chronic pyelonephritis.
11. Butler[46] showed a similar relationship in children of hypertension and pyelonephritis in fifteen of his cases.
12. Weiss and Parker,[47] 1938, in 100 cases of pyelonephritis showed a relationship between the degree of infection and the magnitude of the hypertension. They estimate 15 to 20 per cent of cases of malignant hypertension are due to pyelonephritis.

Unilateral infection—removed surgically followed by changes in blood pressure comparable to the result reported in experimental animals:

1. Butler[46] reports two children with hypertension having unilateral pyelonephritis cured by nephrectomy.
2. Leadbetter[48] mentions two cases of unilateral tuberculosis with readings of 160/100 to 180/100. In one of these the pressure has returned to normal since operation.
3. Barker and Walters[49] review a case with immediate return of blood pressure to normal after removal of an infected kidney, the site of a stone, 13 years previously.
4. Author's case had a kidney stone known to be present 16 years. With nephrectomy a definite fall of blood pressure was noted. Although this did not return to a normal level, disappearance of headaches and improvement in hearing followed removal of the poorly functioning kidney (Published elsewhere).
5. Longcope,[45] reporting a case with a stone impacted in one of the calices and accompanied by pyelonephritis and hypertension, makes note of the fact that with infection, hypertension comes long before there is any evidence of renal insufficiency.

II. *Extrinsic,* effecting interference with the renal artery circulation:

MALPOSITION IS WELL EXEMPLIFIED IN THE CASE OF:

1. Leadbetter and Burkland[50] report an ectopic kidney located in the pelvis causing constriction and stretching of the renal vessels with subsequent hypertension. Nephrectomy resulted in a cure.

HYDRONEPHROSIS HAS BEEN SEEN NOT INFREQUENTLY WITH BLOOD PRESSURE CHANGES:

1. Löhlein,[51] 1917, reviewed two cases of hydronephrosis with blood pressure readings as high as 210/140.
2. Morton[52] had a definite fall of the blood pressure to normal, in his patient following nephrectomy for a hydronephrotic kidney with an anomalous vessel.
3. Nesbit[53] has reported several interesting cases in both this and the infectious group.

ARTERIOSCLEROTIC PLAQUES WITHIN THE RENAL BLOOD VESSELS NO DOUBT OFTEN INTERFERE WITH RENAL CIRCULATION:

1. Freeman and Hartley[54] observed a case in which a single kidney was made ischemic and hypertension resulted due to an atheromatous plaque at the entrance of renal artery.

THROMBOSIS OF THE RENAL ARTERY MAY ACCOUNT FOR MANY CASES, A FEW OF WHICH HAVE BEEN RECOGNIZED:

1. Boyd and Lewis'[55] case showed a huge infarct in the kidney with marked hypertension. Nephrectomy resulted in a return of blood pressure to 124/84.
2. Welty[56] reviews a group of eleven cases dying with thrombosis of the renal artery all of which were hypertensive.
3. The unilateral contracted kidney with hypertension seems a very likely end result where the condition has partially healed by recanalization of the vessel.

THE STUDY (CLINICAL)

The value of experimental work depends on the way it can be applied clinically. Is it not true, that our fastest aeroplanes are often designed by capable pilots? Having learned the theoretical mechanics of hypertension from the physiologists, the pilots or clinicians are stepping into the field with new designs or application for this knowledge. They are fitting surgery and urological treatment to the relief of a certain group of these patients. If removal of the ischemic kidney in the experimental animal allows blood pressure to return to normal, the same should result in the human. In our kidneys no silver clamp has been applied, but infection has applied thousands of clamps to the smaller blood vessels. Abnormal position and pathological conditions have likewise constricted the renal artery. We may classify the clinical situations as outlined in Table I.

The Future

Large groups of cases with hypertension have been reviewed in an attempt to correlate the urinary tract findings and blood pressure readings. Schroeder and Steele[57] in 71 cases of essential hypertension demonstrated some abnormality in the intravenous urography in 50. Their reported data is as follows:

I. Lesions suggesting obstruction to the flow of urine were found in 36 patients:

a) There was well marked bilateral hydronephrosis in 4.
b) Moderate hydronephrosis bilateral in 7.
c) Unilateral hydronephrosis present in 20.
d) " " moderate in 11.
e) " " mild in 9.
f) Hydronephrosis mild or moderate associated with disease of the other kidney as follows:

1. Marked inflammatory contraction and distortion of the renal pelvis.
2. Marked ptosis.
3. Total absence of function.
4. Replacement of the kidney by calcified cysts.

g) Hydroureter, five patients.
h) Double kidney with mild unilateral hydronephrosis.

II. Renal Calculi were seen in five patients:

a) In pelvis or calices.
b) Associated with hydronephrosis.
c) Combined with total absence of function of the opposite kidney.

III. Miscellaneous lesions were also noted:

a) Absence of evidence of function by excretion of dye for intravenous urography, four patients.
b) Two patients with ptosis of one kidney.
c) Bilateral duplication of kidneys and ureters.
d) Marked distortion of calices perhaps the result of old inflammation.
e) Persistent sharp angulation of the ureter.

TABLE II

MAHER AND WOSIKA[55] SUMMARIZE 101 CASES SHOWING THE FOLLOWING: PRIMARY URINARY TRACT PATHOLOGY ALL ASSOCIATED WITH HYPERTENSION

Prostatic obstruction including complications of upper urinary tract	31
Chronic pyelonephritis with complications	27
Renal stone and complications	18
Prolapse of uterus with hydronephrosis and infection	7
Diverticula of bladder and complications	5
Urethral stricture (male)	4
Cancer of bladder with ureteral obstruction and infection	2
Renal tumors	2
Congenital cystic kidneys	2
Bladder stone	1
Congenital absence of kidney	1
Vesicovaginal fistula	1

The experimental work and the clinical examples mentioned above are a distinct challenge to every enterprising and thinking man of medicine. It becomes a problem to see which patients fall into the group that can be cured by surgery or urologic treatment.

Urology has gone far as a specialty with the addition of the x-ray and the kidney function tests, but as yet these leave much to be desired and there is great need for an accurate method to evaluate carefully and easily the kidney function early in the disease. At the present time we have no explanation of the fact that some patients with pyelonephritis develop hypertension before renal insufficiency while some develop it only after renal damage has become marked and still others die of uremia with very little hypertension.

It is evident that hypertensive disease can be divided into at least two categories. One contains that group of cases in which there is local inflammatory, suppurative or obstructive impairment of one or both kidneys, causing hypertension. The second group contains those instances of so-called essential hypertension in which no local renal factor has as yet been demonstrated. Reduction of hypertension by nephrectomy has been accomplished in those cases where infection was the cause of lessened renal blood flow. Study of the blood vessels in the second

group shows a hypertonus of the efferent glomerular arterioles that tends to produce a degree of renal ischemia.[59] Paunz[60] showed in the dog that a new blood supply to the kidney can be supplied by omentopexy, the vascularization thereby effected being adequate to maintain urine formation after ligation of the artery of the operated kidney and even after removal of the opposite kidney. This procedure suggests that we may have an approach to the problem of treatment of this type of case in the human. It is a problem that can only be approached cautiously after a thorough knowledge of filtration rate, renal blood flow and mass of tubular excretory tissue.[61] It is an established fact that the formation of urine is by a combination of three processes. The first, a filtration process, takes place in the glomerulus. The second, the protein-free filtrate passes on down to the tubules where the water and valuable constituents as chloride and glucose are reabsorbed. A third process, which is perhaps the most important, is that of tubular excretion.[62] So complete is this process that excretion of many substances result in almost completely removing them from the plasma before the blood reaches the renal veins. The tubular excretion removes about 94 per cent of phenolsulphonphthalein, while only about 6 per cent is removed by glomerular filtration. The organic iodine preparations (diodrast, hippuran and iopax) have this same characteristic way of removal. So it is easy to see that it is possible to measure quantatively the amount of intact tubular epithelium of the kidney by measuring the rate of excretion of the dye or chemical. Here two practical difficulties arise, in that these latter substances must be given by continuous intravenous infusion in order to maintain a constant plasma concentration; and the analysis of urinary secretion of diodrast and hippuran is at present a tedious and difficult matter. However, we hope that simpler methods of measuring the renal blood flow will be available in the future. It would seem that since tubular excretion carries 94 per cent of the load, glomerular filtration is relatively unimportant, so we need not be concerned with a substitute for normal vascularization in consideration of the value of omentopexy. It is the opinion of competent observers[61] that man can get along with a very small residue of glomerular function, providing the complicating features of renal destruction are eliminated. These complicating features might in a considerable measure be eliminated if the accessory blood supply afforded by omentopexy served only to increase the blood flow to the tubules. Crile[63] recently has suggested that renal decapsulation be

done as an adjunct to the operation of celiac ganglionectomy. He feels this procedure has contributed something in addition to the operation he has been championing. I feel no doubt this is due to the increase in renal blood flow by collateral circulation established at the convex surface of the kidney.

So for the future we have the offer of hope to the patient with an infection, be it unilateral, of improvement in his hypertension. If bilateral infection is present urologic treatment with release of obstruction, removal of irritating growths and calculi may give the result desired. Every case of hypertension deserves the right to have thorough urologic investigation before the stamp of incurability is placed upon him. The idea of omentopexy is being studied. Perhaps in time satisfactory study and technique will develop this into a practical procedure. We and our forefathers have erred long in hunting for a magic drug that will reduce pressure. Physiologists and clinicians have brought into the light some facts for understanding this disease. May we in the future look on every case of hypertension with these facts in mind!

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

FEBRUARY 1—*The New York Academy of Medicine.* Executive session; Reading of the minutes. ¶ Papers of the evening —Symposium on allergy—a] Mechanism, Matthew Walzer, Attending in Allergy, Jewish Hospital of Brooklyn; b] Clinical considerations, Robert A. Cooke, Assistant Professor of Clinical Medicine, Cornell University Medical College; c] Allergy in children, Lewis Webb Hill, Associate in Pediatrics, Harvard Medical School; Discussion, Will Cook Spain, Joseph Harkavy. ¶ Report on election of members.

FEBRUARY 15—*The Harvey Society in affiliation with The New York Academy of Medicine.* The Fifth Harvey Lecture, "Physiology of the Renal Circulation," Homer W. Smith, Professor of Physiology, New York University College of Medicine.

SECTION MEETINGS

FEBRUARY 2—*Section of Surgery.* Reading of the minutes. ¶ Presentation of cases —a] Periarteritis nodosa simulating surgical abdomen, Philip Allen; Discussion, Paul Klemperer; b] Successful suture of stab wound of heart, Joseph B. Stenbuck; Discussion, Samuel S. Paley (by invitation); c] Cases illustrating papers of the evening, Samuel A. Thompson, Milton J. Raisbeck. ¶ Papers of the evening—a] The surgical treatment of coronary artery disease with special reference to cardiopericardiopexy, Samuel A. Thompson; Discussion, Henry W. Cave, Frederic W. Bancroft; b] The selection and management of patients in the surgical treatment of coronary disease, Milton J. Raisbeck; Discussion, Charles F. Tenney, Harold J. Stewart. ¶ General discussion. ¶ Executive session.

FEBRUARY 6—*Section of Dermatology and Syphilology.* Presentation of cases—a] Vanderbilt Clinic; b] Miscellaneous cases. ¶ General Discussion. ¶ Executive session.

FEBRUARY 8—*Section of Pediatrics.* Reading of minutes. ¶ Papers of the evening—a] Diabetes mellitus in one of identical twins—follow-up studies of both twins, Alfred E. Fischer; Discussion by H. Rawle Geyelin; b] Vitamin A status of children as determined by dark adaptation, Charles Haig (by invitation), Jacques M. Lewis; Discussion by Selig Hecht (by invitation); c] Cystic hygroma in infancy with presentation of three case histories, Abraham Tow; d] A comparative study of therapeutic procedures in scarlet fever at the Kingston Avenue Hospital, Henry Rascoff (by invitation); Sidney Nussbaum (by invitation). ¶ General discussion. ¶ Executive session.

FEBRUARY 13—*Section of Neurology and Psychiatry.* Reading of minutes. ¶ Papers of the evening—a] Report of two cases presenting rhythmic palatal myoclonus, J. T. Dobson (by invitation); Henry Alsop Riley; Discussion, Samuel Brock; b] Dietetic and related studies in multiple sclerosis patients, Richard W. Brickner, Norman Q. Brill (by invitation); with the assistance of Frances H. Naylor, B.Sc., M.A. and Kathryn Montgomery, B.Sc.; Discussion, Tracy J. Putnam (by invitation); Israel S. Wechsler; c] Hemangioblastoma of the cerebellum. Clinical, surgical and roentgenological aspects, Leo M. Davidoff, Cornelius G. Dyke; Discussion, Henry Alsop Riley, Charles Davison. ¶ Executive session.

FEBRUARY 14—*Special Meeting on Syphilis of the Section of Dermatology and Syphilology.* Presentations — a] Unusual cases of skin, visceral and neurosyphilis; b] Complications arising from syphilis.

FEBRUARY 16—*Section of Orthopedic Surgery.* Reading of the minutes. ¶ Presentation of cases—Chondral fracture of the patella, Joseph E. Milgram (by invitation). ¶ Papers of the evening—a] Delayed reduction of fractures, John R. Moore, Philadelphia (by invitation); Discussion, Mather Cleveland; b] Resection of the elbow, B. Franklin Buzby, Camden (by invitation); Discussion, Philip D. Wilson; c] Injury to the femoral cartilage by the medial meniscus, Alan DeForest Smith, Byron B. King (by invitation). ¶ General discussion. ¶ Executive session.

FEBRUARY 19—*Section of Ophthalmology.* Instruction hour 7:00 to 8:00. Nonsuppurative diseases of the cornea, part II, Ralph I. Lloyd. Demonstration of Slit Lamp Cases 8:00 to 8:30, Gordon M. Bruce, Girolamo Bonaccolto, Milton Berliner. ¶ Reading of the minutes. ¶ Presentation of cases—a] A self-setting cross cylinder, Joseph I. Pascal; b] The intramarginal suture in lid repair, Henry Minsky; c] Four cases of unusual traumatic stationary cataracts, Daniel M. Rolett (by invitation); d] Pseudotumor of the orbit, Willis Knighton. ¶ Papers of the evening—a] Intravital color of the macula, Johan W. Nordenson, Stockholm (by invitation); b] Harvey Cushing: An ophthalmologist's appreciation, Bernard Samuels. ¶ General discussion. ¶ Executive session.

FEBRUARY 20—*Section of Medicine.* This meeting was held at the Einhorn Auditorium, Lenox Hill Hospital (131 East 76 Street). ¶ Reading of the minutes. ¶ Presentation of cases treated by crymotherapy. ¶ Papers of the evening, Symposium on crymotherapy (so-called artificial hibernation)—a] Rationale and description of method. Conditions treated to date; carcinomata, leukemias, drug addictions. Selection of cases: rejections, acceptances. John C. A. Gerster; b] Cardiovascular aspects, Charles E. Kossmann (by invitation); c] Hematology: (1) Carcinomata, (2) Blood dyscrasias, Carl Reich; d] Blood chemistry, Adolph Bernhard (by invitation); e] Basal metabolism, Jacob Geiger (by invitation); f] Neurological aspects, Thomas K. Davis; g] Temperature observations, Madge C. L. McGuinness; h] Urological observations, H. R. Kenyon; i] Pneumonias, John F. Dixon (by invitation); j] Roentgenological observations, Frank Huber (by invitation); k] Biopsies and deaths (Rudolf M. Paltauf (by invitation); l] Results to date: pain control, clinical manifestations, local treatment (two cases), nursing details, P. K. Sauer (by invitation). Discussion opened by W. Laurence Whittemore. ¶ Inspection of crymotherapy room. Guides were furnished to groups of 6 at 5 minute intervals, Victor Gang (by invitation).

FEBRUARY 21—*Section of Genito-Urinary Surgery.* Reading of the minutes. ¶ Presentation of cases—a] Interstitial cystitis with autopsy findings, Joseph Schwartz, A. Hyman; b] Two unusual pyelograms with operative findings,

George A. Fiedler (by invitation); c] Primary carcinoma of the ureter, M. R. Keen (by invitation); d] Hypernephroma in polycystic kidney with invasion of vena cava, R. B. Henline; e] Unusual bladder tumor of urachal origin, F. C. Hamm; f] Cortical tumor without symptoms, Martin J. Loeb; g] Two cases of long surviving ureteral transplantation, A. R. Stevens; h] Foreign body surrounding penis with suggested new method of removal, D. Makowski (by invitation), H. S. Jeck; i] Embryomatosis of testis, M. M. Melicow (by invitation); j] Micro-aerophilic streptococcus infection of penis and urethra, Paul W. Aschner, Frank L. Meleney. ¶ General discussion. ¶ Executive session.

FEBRUARY 21—*Section of Otolaryngology.* Reading of the minutes. ¶ Papers of the evening—from the Columbia-Presbyterian Medical Center: Nasopharyngeal Tumors—a] Diagnosis (1) Pathological, Arthur P. Stout; (2) Otolaryngological, James W. Babcock; (3) Neurological, Samuel Brock; (4) Roentgenological, Cornelius G. Dyke; b] Treatment, Roentgenological, Haig H. Kasabach (by invitation). ¶ Discussion, Kaufman Schlivek, Rudolph Kramer, Ross Golden, Israel S. Wechsler, Maurice Lenz.

FEBRUARY 27—*Section of Obstetrics and Gynecology.* Reading of the minutes. Program by the Morrisania City Hospital. ¶ Presentation of cases—a] Endometriosis treated with testosterone propionate, Leo Wilson; b] Pregnancy complicated by carcinoma of the cervix (3 cases), Milton J. Goodfriend; c] Eclampsia associated with central placenta previa, Frederick A. Wurzbach, Jr. ¶ Papers of the evening—a] Observations on the use of stilboestrol, Abraham Abarbanel (by invitation). Discussion, Samuel R. M. Reynolds (by invitation); b] Critical analysis of cesarean section at the Morrisania City Hospital, Abraham B. Tamis. Discussion, Harvey B. Mathews, Harry Aranow.

AFFILIATED SOCIETIES

FEBRUARY 17—*Joint Meeting of New York Roentgen Society and Philadelphia Roentgen Ray Society* at Memorial Hospital, 444 East 68 Street. Ralph E. Herendeen, Chairman; Introductory remarks, C. P. Rhoads, Director of Memorial Hospital (Introduced by Dr. James Ewing). ¶ Papers of the evening—a] Some new problems in radiology, James Ewing; b] The relation of dosage in roentgens to size of portal, Hayes Martin; c] Diagnosis and treatment of cancer of the lung, Lloyd Craver; d] Treatment of artificial menopause, Gray H. Twombly; e] Serum phosphotase studies as an aid in radiation therapy of bone tumors, Helen Q. Woodard.

FEBRUARY 29—*New York Pathological Society (in affiliation with The New York Academy of Medicine).* Case reports—a] Cruveilhier-Baumgarten cirrhosis of the liver, Amour F. Liber, Chester R. Brown; b] Multiple hemangioendotheliomata of lung, Alfred Plaut. ¶ Papers of the evening—a] Correlation between clinical and experimental findings in cases showing invasion of the blood stream by staphylococci, Bernard Kleiger (by invitation), John E. Blair (by invitation); b] Pathological changes of the nervous system in chronic alcoholism, Lewis D. Stevenson (by invitation).

IN MEMORIAM

Hans Horst Meyer

The New York Academy of Medicine regrets to inform its fellowship of the death on October 8, 1939, of one of its most distinguished honorary fellows, Professor Hans Horst Meyer of Vienna. His association with the Academy began thirty-five years ago when his scientific contributions in pharmacology resulted in an invitation from the Harvey Society to deliver the first Harvey lecture in the Academy on October 7, 1905 on the Meyer-Overton theory of anesthesia.

Hans Horst Meyer was born at Insterburg (East Prussia) March 17, 1853; studied at the Universities of Koenigsberg, Leipzig and Berlin; graduated in medicine from the University of Koenigsberg in 1877; elected an Honorary Fellow of the Academy November 5, 1936. Introduced to the methods and literature of physiology by Max Jaffé at the University of Koenigsberg, he later became assistant in pharmacology to Oswald Schmiedeberg in Strasbourg.

In 1882, when 28 years of age, he was called to the professorship of pharmacology at the University of Dorpat (then Russia, now Estonia). In 1884 and for a period of twenty years thereafter, he occupied the chair in pharmacology at the University of Marburg, with such distinguished associates as the pathologist Ludwig Aschoff and the internist Friedrich Mueller. It was during this time that many of his fundamental contributions to pharmacology were made.

In 1904, he became professor of experimental pharmacology at the University of Vienna where he continued to serve until his retirement in 1924. In a period when the teaching of pharmacology was largely didactic, he first employed the experimental method of instruction.

In 1908, he refused a call to the professorship in Berlin, preferring to remain in Vienna as head of the distinguished Institute for Experimental Pharmacology. Here came numerous pupils from all parts of the world. Among his American pupils were Dr. George Whipple, now Professor of Pathology and Dean of the Medical School of the University of Rochester, Dr. Henry Gray Barbour, now Professor of Pharmacology at Yale University, and many other outstanding investigators. He is well known to most American physicians and students because of the comprehensive work, "Die Experimentelle Pharmakologie als Grundlage der Arzneibehandlung," which was published in collaboration with Professor Gottlieb of Heidelberg and later with his pupil and successor, Professor Ernst Peter Pick, who is now a resident of New York. An English translation of the eighth edition of this classic work was published in 1932. His latest work "Hypnotica" in collaboration with E. P. Pick, appears in "Handbuch der Normalen und Pathologischen Physiologie," vol. 17, Berlin 1926.

Aside from the many honors which came to him during the course of his long and fruitful career, such as the honorary fellowship in the Academy and in many other scientific societies, he was the recipient of honorary degrees from the Universities of Vienna, Koenigsberg, Marburg, St. Andrews and Edinburgh. Professor Meyer's greatest achievement lies in having related pharmacology to biology and in establishing pharmacology as the basis of rational drug therapy. His influence upon experimental pharmacology will never be fully appreciated because of his scientific generosity and his modesty. The Institute of Experimental Pharmacology in Vienna had the most delightful atmosphere of mutual helpfulness and high endeavor. The lives of all who had the privilege of working under his guidance

were permanently affected by this spirit of scientific fellowship. He was beloved by all his students and associates in Vienna where he exerted a marked influence upon the entire faculty of medicine.

In characteristic fashion, retirement at the age of seventy failed to dim his scientific and professional ardor. For years thereafter, he continued to work in his institute, guiding the scientific work of the younger assistants. Like his great American colleague, William Henry Welch, the period of retirement from academic work in his chosen field served merely to open new vistas of useful activity. During the World War and for some years thereafter he spent much of his time in the study of cardiovascular physiology and therapeutics at the famous Heart Station in Vienna where he had an opportunity in his later years to apply his knowledge of physiology and pharmacology more directly to the care of the sick.

The political turmoil of recent years and its destructive effect upon Viennese medicine saddened the last year of his life. Until the end, his true nobility of character and his interest and love for his associates and friends remained undaunted.

GEORGE BAEHR.

DEATHS OF FELLOWS

MEYER, HANS HORST: born at Insterburg (East Prussia), March 17, 1853; died in Vienna, October 8, 1939; studied at the Universities of Koenigsberg, Leipzig and Berlin; graduated in medicine from the University of Koenigsberg in 1877; elected an Honorary Fellow of the Academy November 5, 1936.

Introduced to the methods and literature of physiology by M. Jaffé at the University of Koenigsberg, he later went to O. Schmiedeberg at the University of Strassburg under whose direction he soon advanced to the position of assistant. In 1881 he qualified for a lectureship in phamracology at the University of Strassburg. In the same year he was appointed professor at the University of Dorpat (then Russia, now Estonia). In 1884 he removed to Marburg where he taught for twenty years. During that period he accepted several invitations to give lectures in England and America. In 1904 he assumed the professorship of pharmacology at the University of Vienna, which he retained until his retirement in 1924.

Dr. Meyer's greatest achievement lies in having established a close link between pharmacology and biology, and in having made pharmacology the basis of a rational medicinal therapy. His comprehensive work "Die Experimentelle Pharmakologie als Grundlage der Arzneibehandlung," Berlin and Vienna, 1910, published in collaboration with R. Gottlieb (with an English translation of the 8.ed., 1932) is considered a classic. His latest work "Hypnotica" (in collaboration with E. P. Pick) appears in "Handbuch der Normalen und Pathologischen Physiologie," vol. 17, Berlin 1926.

VAN COTT, JOSHUA MARSDEN: 160 Henry Street, Brooklyn, New York; born in New York City, June 12, 1861; died in Brooklyn, New York, February 8, 1940; graduated in medicine from the Long Island College Hospital in 1885; elected a Fellow of the Academy November 1, 1906.

Dr. Van Cott had practiced in Brooklyn for fifty-four years and was emeritus professor of pathology and clinical medicine at the Long Island College of Medicine; senior physician to the Brooklyn Hospital; consulting physician to the Kings County, St. John's, Methodist Episcopal and Wyckoff Heights Hospitals; consulting pathologist

to the Brooklyn State and Long Island College Hospitals; president of the professional staff of the Brooklyn Hospital, and president of the Board of Trustees of the Hoagland Laboratory of the Long Island College of Medicine.

He was a Fellow of the American Medical Association, a Fellow of the American College of Physicians, a member of the New York Pathological Society, a member and former president of the Medical Society of the County of Kings (1909), and a member of the New York State Medical Society and chairman of its Public Health and Education Committee, 1912-1925 and its vice-president, 1927-1928.

WILNER, ANNA SAMONILOVNA: 246 Beach 122 Street, Rockaway Park, Queens, New York; born in Smoliana, Mogileff, Russia, August 26, 1874; died in Rockaway Park, Queens, February 10, 1940; graduated in medicine from the Woman's Medical College of the New York Infirmary in 1895; elected a Fellow of the Academy December 7, 1905.